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Supporting Information

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Highly Stereoselective Nucleophilic Difluoromethylation Using Difluoromethyl Phenyl Sulfone: Facile Synthesis of Chiral a-Difluoromethyl Amines from *N*-(*tert*-Butylsulfinyl)aldimines

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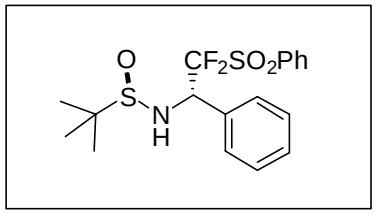
General:

Unless otherwise mentioned, solvents and reagent were purchased from commercial sources and used as received. THF was freshly distilled over sodium. Difluoromethyl phenyl sulfone and *N-tert*-butanesulfinyl were prepared using known procedures. ^{1}H NMR spectra were recorded on Bruker 300 or Mercury 300 spectrometers with Me_4Si as internal standard. ^{19}F NMR spectra were recorded on Bruker 300 or Mercury 300 spectrometers with $CFCl_3$ as external standard. ^{13}C NMR spectra were recorded on Bruker 300 , Avance 500 or DPX-400 spectrometers. Mass spectra were obtained on a HP5989A spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the EI , ESI or MALDI mode.

Typical procedure for Stereoselective Nucleophilic Difluoromethylation Using Difluoromethyl Phenyl Sulfone:

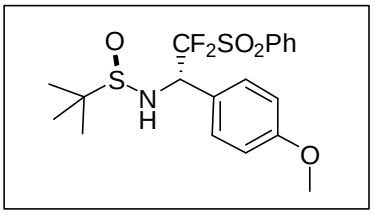
Under N_2 atmosphere, into a 20-mL Schlenk flask containing *N*-(*tert*-butylsulfinyl)aldimine(**6a**) (440 mg, 2.1 mmol) and $PhSO_2CF_2H$ (385 mg, 2.0 mmol) in THF (10 mL) at –78 ^{o}C, was added a THF solution (2.2 mL) of $(TMS)_2NLi$ (LHMDS, 1.06M, 2.4mmol). The reaction mixture was then stirred at this temperature for 20 min, followed by adding a saturated NaCl aqueous solution (10 mL) at this temperature. The solution mixture was extracted with EtOAc (25 mL x 3), and the combined organic phase was dried over $MgSO_4$. After the removal of solvents under vacuum, the crude product was further purified by silica gel column chromatography to give product **7a** as a white solid, yield: 95% (763mg).

(Rs)-N-[(S)-2,2-Difluoro-1-phenyl-2-(phenylsulfonyl)ethyl]-2-methylpropane-2-sulfinamide (**7a**):



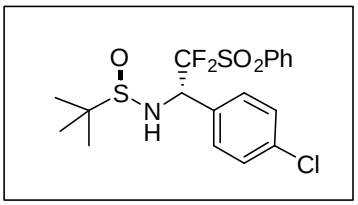
White solid. mp 144-146°C; $[a]_D^{25}$ = –27.4 (c = 0.8, $CHCl_3$). IR (film): 3066, 2962, 1584, 1449, 1349, 1158, 1087cm^{-1}. ^1H NMR: d7.89 (d, *J* = 7.5 Hz, 2H), 7.70–7.75 (m, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.37–7.44 (m, 5H), 5.24–5.36 (m, 1H), 4.04 (d, *J* = 7.8 Hz, 1H), 1.29 (s, 9H). ^{19}F NMR:d–102.51 (dd, *J* = 235.5, 8.7 Hz, 1F), –108.55 (dd, *J* = 235.5, 15.1Hz, 1F). ^{13}C NMR:d135.29, 133.40, 133.30, 130.46, 129.59, 129.26, 128.89, 128.75, 121.06 (t, *J* = 292.0 Hz), 60.72 (dd, *J* = 23.5, 19.4Hz), 57.37, 22.40. MS (EI, m/z, %): 402 (M^++1, 1.2), 140 (100.0). Elemental Analysis (EA): calcd. for $C_{18}H_{21}F_2NO_3S_2$: C, 53.85; H, 5.27; N, 3.49; Found: C, 53.67; H, 5.33; N, 3.35.

(Rs)-N-[(S)-2,2-Difluoro-1-(4-methoxyphenyl)-2-(phenylsulfonyl)ethyl]-2-methylpropane-2-sulfinamide (**7b**):



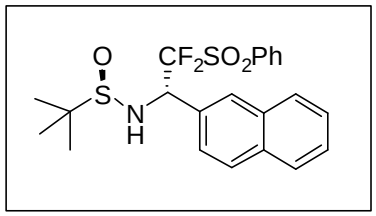
White solid. Mp 108–110°C. $[a]_D^{25}$ = –20.7 (c = 0.7, $CHCl_3$). IR (film): 2961, 1612, 1585, 1516, 1158 cm^{-1}. ^1H NMR: d7.88 (d, *J* = 7.5 Hz, 2H), 7.68–7.73 (m, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.35 (d, *J* = 8.7Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.18–5.29 (m, 1H), 3.95 (d, *J* = 8.4 Hz, 1H), 3.79 (s, 3H), 1.27 (s, 9H). ^{19}F NMR: d–102.84 (dd, *J* = 236.3, 11.0 Hz, 1F), –108.10 (dd, *J* = 236.3, 15.8 Hz, 1F). ^{13}C NMR:d160.44, 135.20, 133.42, 130.39, 129.98, 129.18, 125.19, 121.07 (t, *J* = 291.2 Hz), 114.30, 60.13 (dd, *J* = 23.8, 19.6 Hz), 57.24, 55.21, 22.34. MS (EI, m/z, %): 433(M^++2, 6.3), 170(100.0). EA: calcd. for $C_{19}H_{24}F_2NO_4S_2$: C, 52.88; H, 5.37; N, 3.25; Found: C, 52.76; H, 5.46; N, 3.09.

(Rs)-N-[(S)-1-(4-Chlorophenyl)-2,2-difluoro-2-(phenylsulfonyl)ethyl]-2-methylpropane-2-sulfinamide (**7c**):



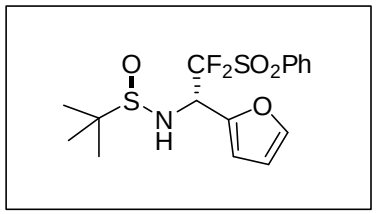
White solid. Mp 135-137°C. $[\alpha]_D^{25}$ = –17.8(c = 0.6, $CHCl_3$). IR (film): 2962, 1584, 1494, 1448, 1349, 1158cm^{-1}. ^1H NMR:δ7.90 (d, *J* = 7.8 Hz, 2H), 7.74 (t, *J* = 7.5Hz, 1H), 7.59 (t, *J* = 7.8Hz, 2H), 7.34–7.41 (m, 4H), 5.22–5.34 (m, 1H), 4.06 (d, *J* = 8.7 Hz, 1H), 1.29 (s, 9H). ^{19}F NMR: δ–102.49 (dd, *J* = 238.0, 9.6 Hz, 1F), –108.88 (dd, *J* = 238.0, 18.0 Hz, 1F). ^{13}C NMR:δ135.68, 135.39, 133.08, 131.74, 130.40, 130.07, 129.27, 129.06, 120.71 (t, *J* = 292.5 Hz), 60.12 (dd, *J* = 24.2, 19.7 Hz), 57.42, 22.29. MS: (ESI, m/z): 436 (M^++1). EA: calcd. for $C_{18}H_{20}ClF_2NO_3S_2$: C, 49.59; H, 4.62; N, 3.21; Found: C, 49.57; H, 4.72; N, 3.04.

(Rs)-N-[(S)-2,2-Difluoro-1-(naphthalen-2-yl)-2-(phenylsulfonyl)ethyl]-2-methylpropane-2-sulfinamide (**7d**):



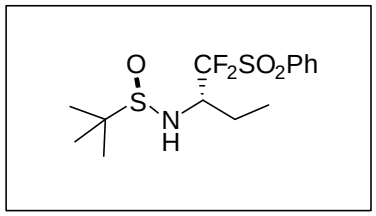
White solid. Mp 125-126°C. $[\alpha]_D^{25}$ = –5.6 (c = 1.0, $CHCl_3$). IR (film): 3062, 2961, 1601, 1583, 1448, 1347, 1157, 1085 cm^{-1}. ^1H NMR: δ7.78–7.93(m, 6H), 7.60–7.66 (m, 1H), 7.45–7.52 (m, 5H), 5.41–5.53(m, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 1.29 (s, 9H). ^{19}F NMR: δ–102.70 (dd, *J* = 238.5, 10.1 Hz, 1F), –108.74 (dd, *J* = 238.5, 15.5 Hz, 1F). ^{13}C NMR:δ 135.18, 133.62, 133.25, 132.97, 130.54, 130.36, 129.11, 128.94, 128.80, 128.30, 127.62, 126.89, 126.49, 125.16, 121.15 (t, *J* = 292.3 Hz), 60.82 (dd, J = 24.1, 19.4 Hz), 57.34, 22.34. MS (EI, m/z, %): 454 (M^++3, 1.4), 190 (100.0). HRMS (ESI): calcd. for $C_{22}H_{23}F_2NO_3S_2Na$(M^++Na): 474.0979625; Found: 474.0979510.

(Rs)-N-[(S)-2,2-Difluoro-1-(furan-2-yl)-2-(phenylsulfonyl)ethyl]-2-methylpropane-2-sulfinamide (**7e**):



White solid. Mp 136-138°C. $[a]_D^{25}$: = –45.5(c=1.0, $CHCl_3$). IR (film): 2962, 1584, 1500, 1475, 1449, 1349, 1191cm^{-1}. ^{1}H NMR: d7.92 (d, *J* = 7.8 Hz, 2H), 7.72–7.78 (m, 1H), 7.60 (t, *J* = 7.8Hz, 2H), 7.45 (d, *J* = 1.8 Hz, 1H), 6.56 (d, *J* = 3.3 Hz, 1H), 6.39–6.40 (m, 1H), 5.31–5.43 (m, 1H), 4.06 (d, *J* = 9.3 Hz, 1H), 1.29 (s, 9H). ^{19}F NMR: d–103.55 (dd, *J* = 237.7, 13.5Hz, 1F), –107.54 (dd, *J* = 237.7, 16.0 Hz, 1F). ^{13}C NMR:d145.77, 143.94, 135.32, 133.25, 130.42, 129.27, 120.15 (t, *J* = 293.5 Hz), 111.34, 110.85, 57.40, 55.24 (dd, J = 24.5, 21.8 Hz), 22.36. MS (EI, m/z, %): 392 (M^++1, 0.8), 57(100.0). EA: calcd. for $C_{16}H_{19}F_2NO_4S_2$: C, 49.09; H, 4.89; N, 3.58; Found: C, 49.05; H, 5.18; N, 3.45.

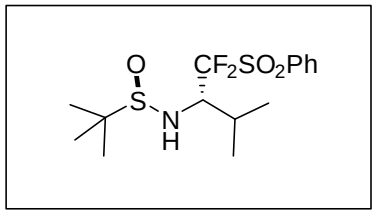
(Rs)-N-[(S)-1,1-Difluoro-1-(phenylsulfonyl)butan-2-yl]-2-methylpropane-2-sulfinamide (**7f**):



White solid. Mp 112-114 °C. $[a]_D^{25}$ = –25.0 (c = 0.8, $CHCl_3$). IR (film): 2965, 1584, 1449, 1337, 1164 cm^{-1}. ^{1}H NMR:d7.96 (d, *J* = 7.8 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 2H), 3.93–4.08 (m, 1H), 3.43 (d, *J* = 8.7 Hz, 1H), 2.17–2.28 (m, 1H), 1.76–1.92 (m, 1H), 1.26 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR: d–103.93 (dd, *J* = 231.5,

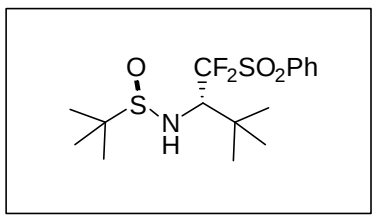
10.1 Hz, 1F), 105.00 (dd, *J* = 231.5, 12.0 Hz, 1F). ^{13}C NMR:δ135.35, 133.57, 130.46, 129.32, 121.77 (t, *J* = 292.5 Hz), 60.69 (t, *J* = 20.4Hz), 57.13, 23.92 (d, *J* = 3.4 Hz), 22.58, 10.27. MS (EI, m/z %): 354 (M^++1, 4.3), 57 (100.0). HRMS (MALDI): Calcd. for $C_{14}H_{22}NO_3S_2$ (M^++1): 354.10037; Found: 354.1007.

(Rs)-N-[(S)-1,1-Difluoro-3-methyl-1-(phenylsulfonyl)butan-2-yl]-2-methylpropane-2-sulfinamide (**7g**):



White solid. Mp 120-121°C. $[\alpha]_D^{25}$ = –54.3 (c = 0.9, $CHCl_3$). IR (film): 2964, 1584, 1475, 1449, 1345, 1164 cm^{-1}. ^{1}H NMR:δ7.96 (d, *J* = 7.5 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 2H), 4.01–4.15 (m, 1H), 3.43 (d, *J* = 9.9 Hz, 1H), 2.56–2.63 (m, 1H), 1.27 (s, 9H), 1.22 (d, *J* = 6.9Hz, 3H), 1.06 (d, *J* = 6.9Hz, 3H). ^{19}F NMR: δ–101.63 (dd, *J* = 241.9, 13.2Hz, 1F), –104.59 (dd, *J* = 241.9, 12.4Hz, 1F). ^{13}C NMR:δ135.26, 133.43, 130.44, 129.24, 122.29 (t, *J* = 291.2Hz), 62.53 (t, *J* = 20.0Hz), 57.21, 28.12, 22.54, 20.48, 16.65. MS: (EI, m/z, %): 311 (M^+-57, 21.01), 57(100.0). EA: calcd. for $C_{15}H_{23}F_2NO_3S_2$: C, 49.03; H, 6.31; N, 3.81; Found: C, 49.20; H, 6.29; N, 3.63.

(Rs)-N-[(S)-1,1-Difluoro-3,3-dimethyl-1-(phenylsulfonyl)butan-2-yl]-2-methylpropane-2-sulfinamide (**7h**):



White solid. Mp 105-106°C. $[\alpha]_D^{25}$ = –9.7 (c = 1.0, $CHCl_3$). IR (film): 1584, 1475, 1449, 1347, 1160, 1080 cm^{-1}. ^{1}H NMR:δ7.91 (d, *J* = 7.5 Hz, 2H), 7.70–7.76 (m, 1H), 7.59 (td, *J*

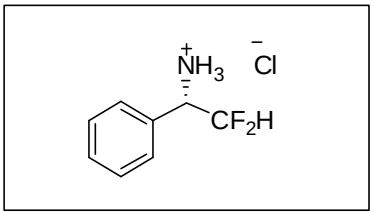
= 7.5, 1.2Hz, 2H), 3.89–4.01 (m, 1H), 3.78 (d, *J* = 9.9 Hz, 1H), 1.31 (s, 9H), 1.20 (s, 9H). ^{19}F NMR: d –90.86 (d, *J* = 236.0 Hz, 1F), –104.33 (dd, *J* = 2360, 16.1Hz, 1F). ^{13}C NMR: d135.06, 133.81, 130.36, 129.14, 122.84 (t, *J* = 291.0 Hz), 65.94 (t, *J* = 21.2 Hz), 57.58, 35.33, 27.88 (t, *J* = 2.2Hz), 22.79. MS (EI, m/z, %): 382 (M^++1, 10.8), 57 (100.0). EA: calcd. for $C_{16}H_{25}F_2NO_3S_2$: C, 50.37; H, 6.61; N, 3.67; Found: C, 50.50; H, 6.55; N, 3.52.

Typical Procedure for Successive Reductive Desulfonylation and Deprotection of the tert-Butylsulfinyl Group:

Under N_2 atmosphere, into a 10-mL flask containing **7a (**180 mg, 0.45 mmol**)** and Na_2HPO_4 (510mg, 3.6 mmol) in 5 mL of anhydrous methanol at –20 °C, was added Na/Hg amalgam (10 wt. % Na in Hg, net sodium content 3.6 mmol). The reaction mixture was stirred at –20°C ~ –10 °C for 1 h. The liquid phase was decanted, and most of the organic phase was removed under vacuum. Then 20 mL of brine was added, followed by extracting with EtOAc. The combined organic phase was dried over $MgSO_4$, and the solvent was removed to give the intermediate product without further purification.

The intermediate product was dissolved in 5 mL of anhydrous methanol. Then 1 mL of HCl/Dioxane (4N) was added. The reaction mixture was stirred at RT for 30 min and was then concentrated to near dryness. Diethyl ether wad added to precipitate out the amine hydrochloride. The precipitate was then filtered off and washed with diethyl ether to provide pure amine hydrochloride **8a,** yield: 83% (72mg).

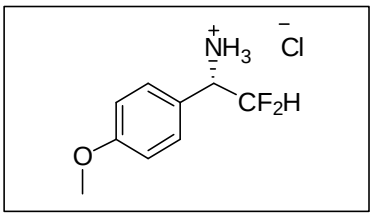
(S)-2,2-Difluoro-1-phenylethanamine hydrochloride (**8a**):



$[a]_D^{25}$ = 25.4 (c = 1.0, CH_3OH). IR (KBr): 2881, 1596, 1509, 1457, 1077 cm^{-1}. ^{1}H NMR (CD_3OD): d7.51(s, 5H), 6.33 (td, J = 54.3, 3.0 Hz, 1H), 4.79–4.85 (m, 1H). ^{19}F NMR (CD_3OD): d–124.56 (ddd, *J* = 285.9, 53.8, 10.4Hz, 1F), –129.37 (ddd, *J* = 285.9, 56.1,

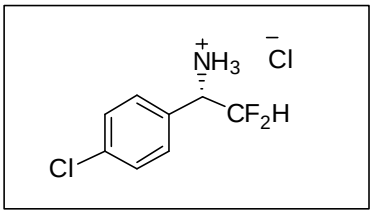
16.0 Hz, 1F). ^{13}C NMR (CD_3OD): d131.88, 131.76 (t, *J* = 2.2Hz), 131.00, 129.90, 115.90 (t, *J* = 244.5 Hz), 57.82 (dd, *J* = 24.3, 21.3 Hz). MS (EI, m/z, %): 156 (0.7, M^+-HCl-1), 106(100.0). HRMS (EI): Calcd. for $C_8H_9F_2N(M^+$-HCl): 157.07031; Found: 157.07106.

(S)-2,2-Difluoro-1-(4-methoxyphenyl)ethanamine hydrochloride(**8b**):



$[a]_D^{25}$ = 26.3 (c = 0.7, CH_3OH). IR (KBr): 2949, 1585, 1521, 1508, 1259, 1186 cm^{-1}. ^{1}H NMR (CD_3OD):d7.46 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7Hz, 2H), 6.30 (td, *J* = 53.7, 2.7 Hz, 1H), 4.73–4.83 (m, 1H), 3.85 (s, 3H). ^{19}F NMR (CD_3OD): d–124.67 (ddd, *J* = 285.3, 53.0, 9.6 Hz, 1F), –131.52 (ddd, *J* = 285.3, 53.5, 17.4 Hz, 1F). ^{13}C NMR (CD_3OD): d 163.15, 131.44, 123.46 (t, *J* = 5.7 Hz), 116.35, 115.99 (t, J = 244.5 Hz), 57.40 (t, *J* = 22.7 Hz), 56.45. MS (ESI, m/z): 188.2 (M^+-Cl). HRMS (ESI) Calcd. for $C_9H_{12}F_2NO(M^+$-Cl): 188.08814; Found: 188.0882.

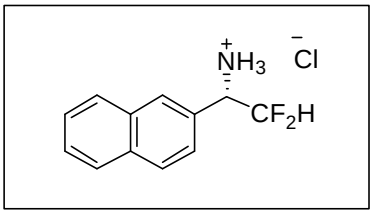
(S)-1-(4-Chlorophenyl)-2,2-difluoroethanamine hydrochloride(**8c**):



$[a]_D^{25}$ = 24.9 (c = 0.5, CH_3OH). IR (KBr): 2858, 1590, 1535, 1497, 1396, 1123, 1057 cm^{-1}. ^{1}H NMR (CD_3OD): d7.53 (s, 4H), 6.34 (td, *J* = 53.4, 3.0 Hz, 1H), 4.83–4.93 (m, 1H). ^{19}F NMR (CD_3OD):d–125.15 (ddd, *J* = 287.0, 53.8, 10.7 Hz, 1F), –131.85 (ddd, J = 287.0, 56.4, 16.0 Hz, 1F). ^{13}C NMR (CD_3OD):d137.81, 131.53, 130.93, 130.38 (d, *J* =

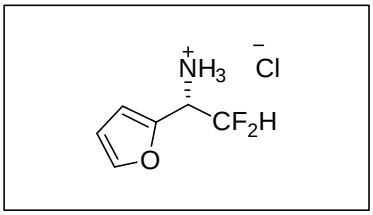
4.4Hz), 115.50 (t, *J* = 244.5Hz), 56.96 (t, *J* = 23.1 Hz). MS (ESI, m/z): 192.1 (M^+-Cl). HRMS (ESI): Calcd. for $C_8H_9ClF_2N$(M^+-Cl): 192.03860; Found: 192.03889.

(S)-2,2-Difluoro-1-(naphthalen-2-yl)ethanamine hydrochloride (**8d**):



$[a]_D^{25}$ = 32.9 (c = 0.6, CH_3OH). IR (KBr): 1588, 1519, 1403, 1051cm^{-1}. ^1H NMR (CD_3OD): d7.92–8.07 (m, 4H), 7.57–7.62 (m, 3H), 6.45 (td, *J* = 53.2, 2.7 Hz, 1H), 4.96–5.08 (m, 1H). ^{19}F NMR (CD_3OD): d–123.91 (dd, *J* = 286.7, 53.0 Hz, 1F), –130.31 (ddd, *J* = 286.7, 55.2, 15.7Hz, 1F). ^{13}C NMR (CD_3OD):d135.52, 134.80, 134.74, 129.97, 129.59, 129.14, 128.89, 128.82, 128.46, 125.95, 115.77 (t, *J* = 244.7 Hz), 57.76 (t, *J* = 23.0Hz). MS (ESI, m/z): 208.1 (M^+-Cl). HRMS (ESI): Calcd. for $C_{12}H_{12}F_2N$(M^+-Cl): 208.09323; Found: 208.09304.

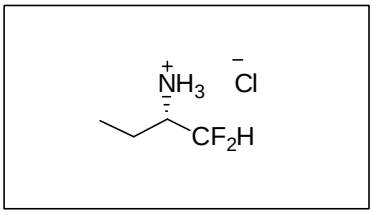
(S)-2,2-Difluoro-1-(furan-2-yl)ethanamine hydrochloride (**8e**):



$[a]_D^{25}$ = 9.2 (c = 0.55, CH_3OH). IR (KBr): 2865, 1589, 1501, 1401, 1150, 1092 cm^{-1}. ^1H NMR (CD_3OD):d7.69–7.70 (m, 1H), 6.73 (d, *J* = 3.6 Hz, 1H), 6.54–6.56 (m, 1H), 6.40 (td, *J* = 53.4, 3.3 Hz, 1H), 5.01–5.10 (m, 1H). ^{19}F NMR (CD_3OD):d–125.74 (ddd, *J* = 288.2, 53.2, 9.0 Hz, 1F), –130.35 (ddd, *J* = 288.2, 54.7, 16.3 Hz, 1F) . ^{13}C NMR (CD_3OD) :d146.74, 144.91 (t, *J* = 3.2 Hz), 114.54 (t, *J* = 244.7 Hz), 113.86, 112.76,

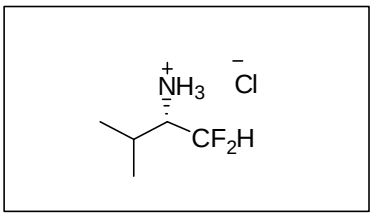
51.77 (dd, *J* = 26.4, 22.8 Hz). MS (ESI, m/z): 148.2 (M^+-Cl). HRMS (EI): Calcd. for $C_6H_7F_2N$ (M^+-HCl): 147.04957; found 147.05016.

(S)-1,1-Difluorobutan-2-amine hydrochloride (**8f**):



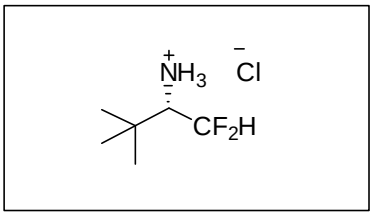
$[a]_D^{25}$ = –19.7 (c = 0.2, CH_3COCH_3). IR (KBr): 2887, 1601, 1525, 1462, 1106 cm^{-1}. ^1H NMR (CD_3OD):d6.22 (td, *J* = 53.7, 2.4Hz, 1H), 3.51–3.66 (m, 1H), 1.67–1.95 (m, 2H), 1.12 (t, *J* = 7.5 Hz, 3H). ^{19}F NMR (CD_3OD): d–127.84 (ddd, *J* = 286.5, 53.5, 7.6 Hz, 1F), –134.33 (ddd, *J* = 286.5, 54.7, 16.4 Hz, 1F). ^{13}C NMR (CD_3OD):d 115.74 (t, *J* = 241.8Hz), 55.36 (t, *J* = 20.6 Hz), 22.00, 9.90. MS (ESI, m/z): 110.3 (M^+-Cl). HRMS (EI): Calcd. for $C_4H_9F_2N$(M^+-HCl): 109.07031; Found 109.07066.

(S)-1,1-Difluoro-3-methylbutan-2-amine hydrochloride(**8g**):



$[a]_D^{25}$ = –26.3 (c=0.3, CH_3COCH_3). IR (KBr): 2948, 1683, 1594, 1515, 1040 cm^{-1}. ^1H NMR (CD_3OD):d6.33 (td, *J* = 54.0, 1.8Hz, 1H), 3.40–3.53 (m, 1H), 2.05–2.17 (m, 1H), 1.13(dd, *J* = 6.6, 2.1Hz, 6H). ^{19}F NMR (CD_3OD): d–125.38 (ddd, *J* = 288.2, 51.8, 6.4 Hz, 1F), –133.42 (ddd, *J* = 288.2, 55.5, 11.8 Hz, 1F). ^{13}C NMR (CD_3OD, 500M):d115.46 (t, *J* = 241.8 Hz), 59.13 (t, *J* = 19.2 Hz), 28.77 (d, *J* = 4.8 Hz), 18.89. MS (ESI, m/z): 124.3 (M^+-Cl). HRMS (EI): Calcd. for $C_5H_{11}F_2N$ (M^+-HCl): 123.08596; Found 123.08658.

(S)-1,1-Difluoro-3,3-dimethylbutan-2-amine hydrochloride (**8h**):

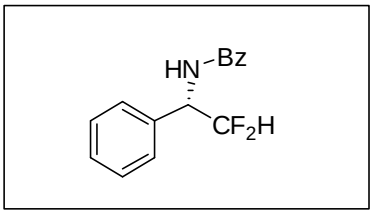


$[\alpha]_D^{25}$ = –17.6 (c = 0.2, CH_3COCH_3). IR(KBr): 2943, 1596, 1526, 1482, 1076 cm^{-1}. ^1H NMR (CD_3OD):δ6.39 (td, *J* = 52.0, 1.5 Hz, 1H), 3.41–3.52 (m, 1H), 1.12 (s, 9H). ^{19}F NMR (CD_3OD): δ–121.05 (dd, *J* = 290.4, 51.6 Hz, 1F), –129.62 (ddd, *J* = 290.4, 52.7, 3.9 Hz, 1F). ^{13}C NMR (CD_3OD, 400M): δ115.51 (t, *J* = 241.1 Hz), 62.40 (t, *J* = 18.1Hz), 33.39 (d, *J* = 5.4 Hz), 27.12 (d, *J* = 1.3 Hz). MS (ESI, m/z): 138.1(M^+-Cl). MS: (EI, *m/z*, %): 122 (14.79, M^+-CH_3), 57 (100.0). HRMS (EI): calcd. For $C_5H_{10}F_2N$ (M^+ - HCl -CH_3) 122.07813; found: 122.07835.

Procedure for Benzoylation of 8a:

Under N_2 atmosphere, a flask containing the amine chloride (**8a**) (0.1 mmol, 19 mg), PhCOCl (0.2 mmol), Et_3N (0.3 mmol) and K_2CO_3 (0.3 mmol) in 2mL dioxane was stirred at 40 °C for 3h. Then removal of the solvents under reduced pressure and flash chromatography afforded **9** quantitatively (26mg) as a white solid.

(S)-N-(2,2-Difluoro-1-phenylethyl)benzamide (**9**):

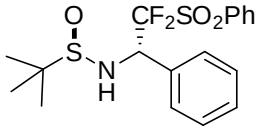


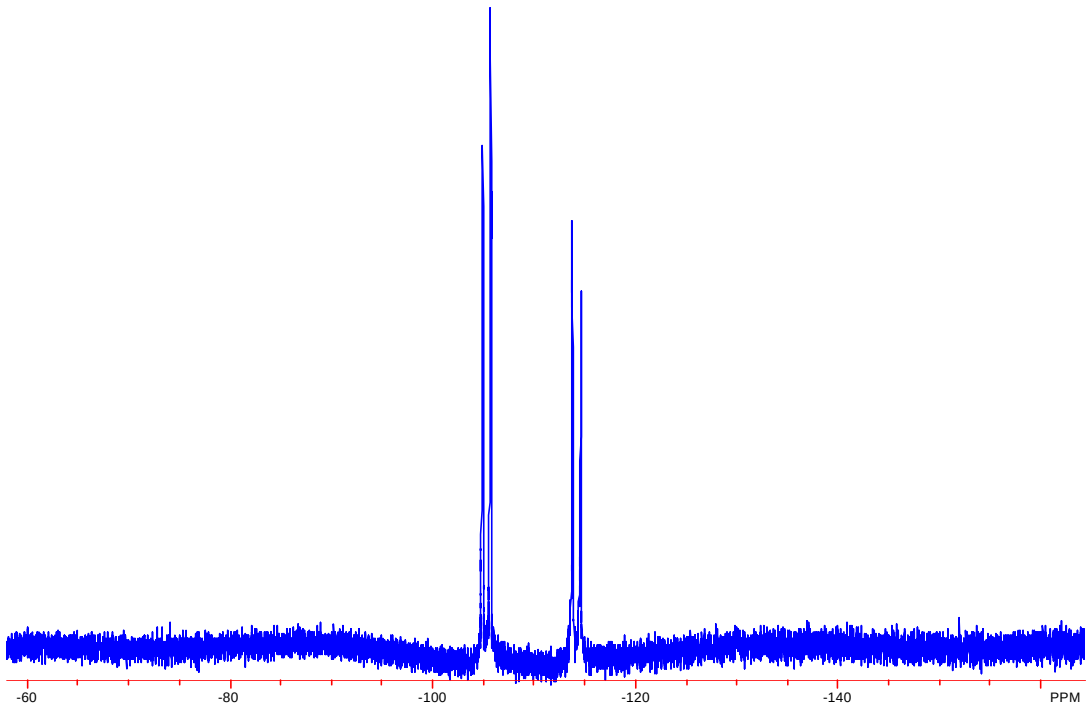
HPLC (Diacel Chiralpak AD-H column, 80:20 hexane/2-propanol; 0.7mL/min; 254 nm; (S)-**9**, r_t= 9.1 min, (R)-**9**, r_t = 14.8min); $[\alpha]_D^{25}$ = –10.8.(c = 0.45, $CHCl_3$); white solid. Mp 153-155°C. IR (film): 3314, 3066, 1640, 1580, 1533, 1490 cm^{-1}. ^1H NMR: δ7.80–7.84 (m,

2H), 7.37–7.57 (m, 8H), 6.74 (d, *J* = 7.5 Hz, 1H), 6.14 (td, *J* = 55.2, 2.1 Hz, 1H), 5.55–5.68 (m, 1H). ^{19}F NMR: d–125.26 (ddd, *J* = 282.1, 56.5, 16.4 Hz, 1F), –128.50 (ddd, *J* = 282.1, 53.6, 13.8Hz, 1F). ^{13}C NMR ($CDCl_3$):d167.20, 134.11 (d, *J* = 4.0 Hz), 133.66, 132.05, 129.00, 128.84, 128.72, 127.86, 127.53, 114.77 (t, *J* = 244.0 Hz), 55.18 (t, *J* = 21.6 Hz). MS (EI, m/z, %): 262 (M^++1, 0.6), 105(100.0). EA: calcd. for $C_{15}H1_3F_2NO$: C, 68.96; H, 5.02; N, 5.36; Found: C, 69.25; H, 5.14; N, 5.30.

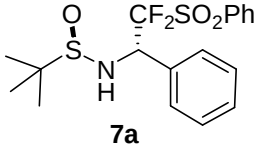
Example of determination of dr ratio of **7a**-**7h** (reaction mixture after saturated NaCl water solution and EtOAc was added) by ^{19}F NMR:

Compound **7a,** one isomer

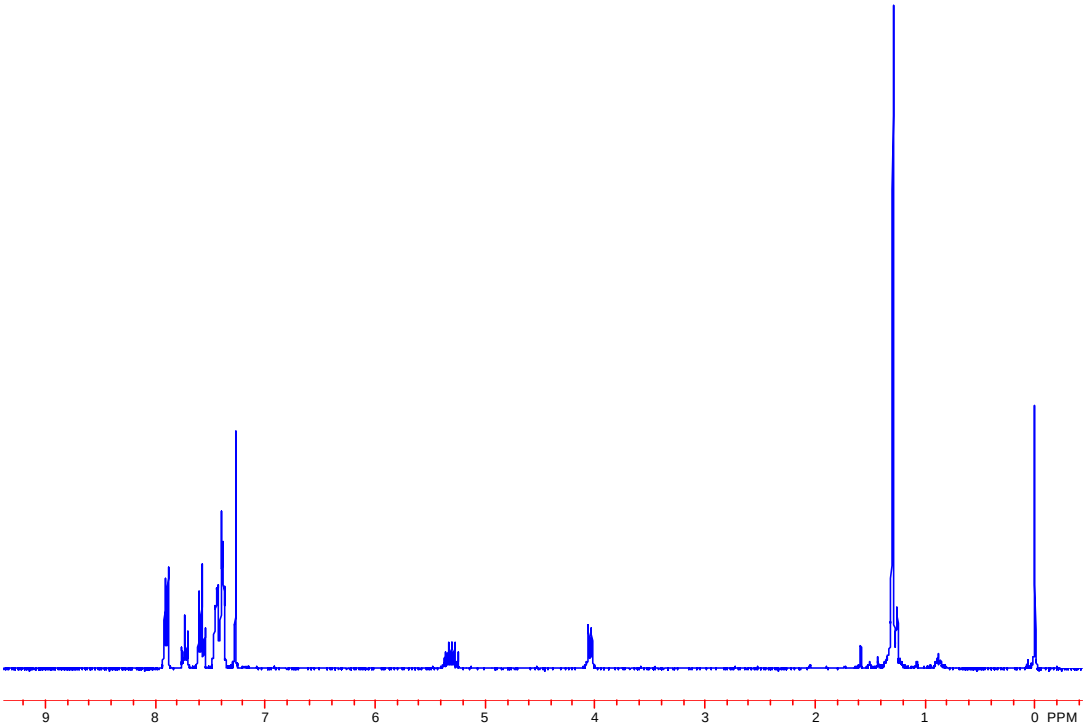




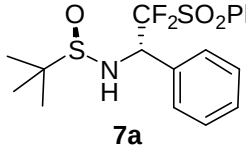
^{1}H NMR($CDCl_3$)



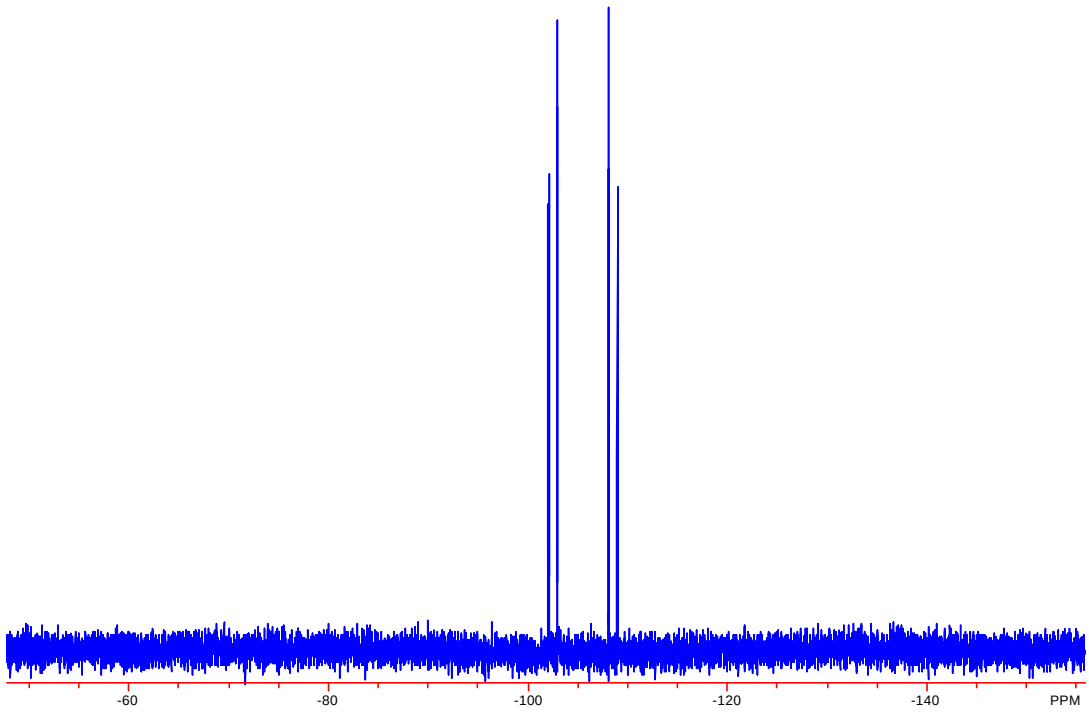
7a



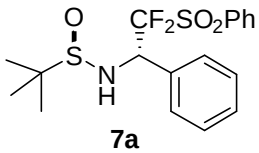
^{19}F NMR($CDCl_3$)



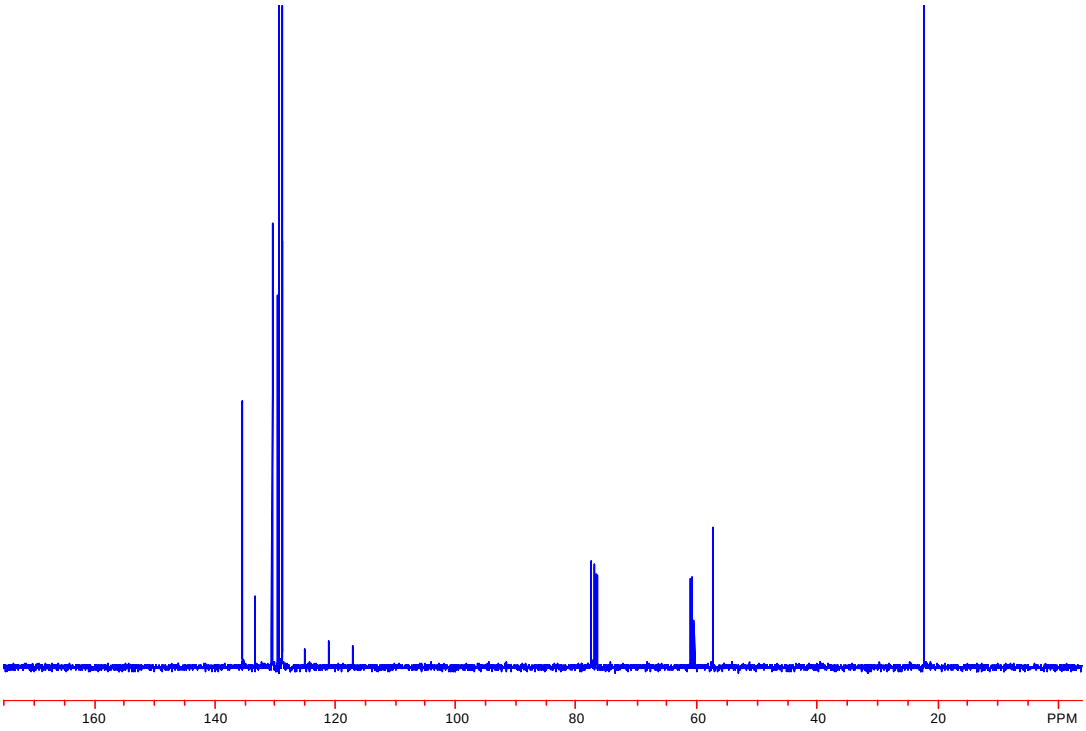
7a


-60
-80
-100
-120
-140
PPM

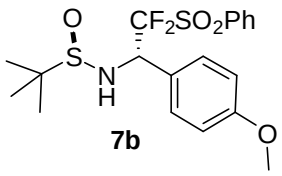
^{13}C NMR($CDCl_3$, 300M)



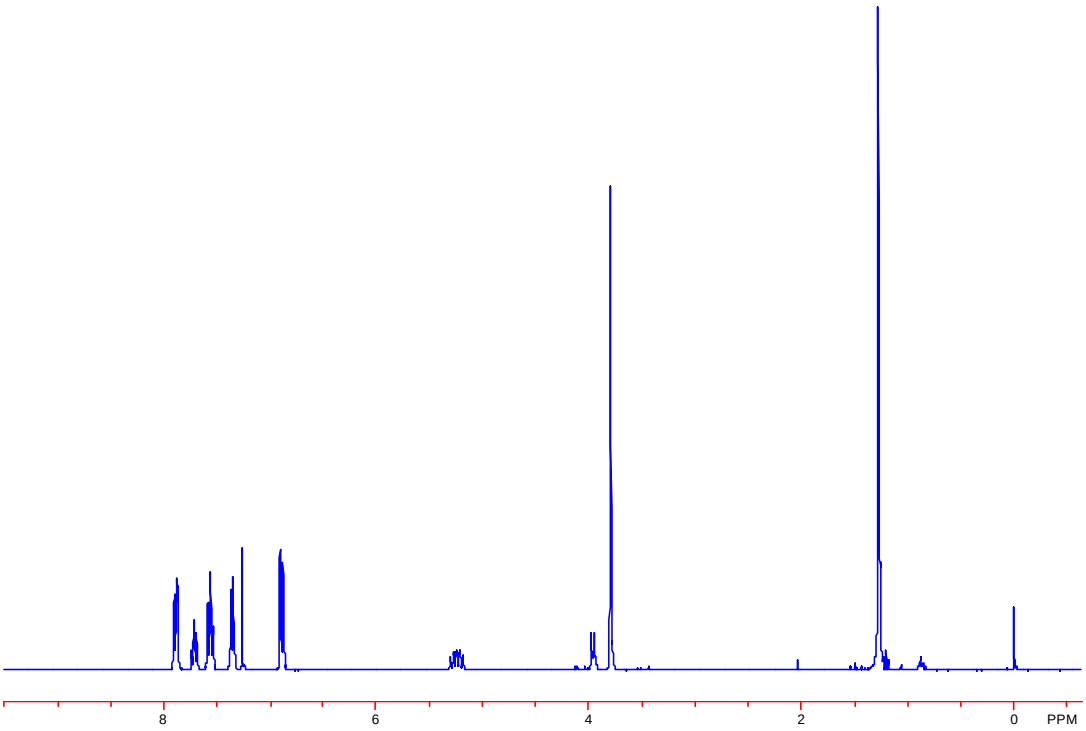
7a

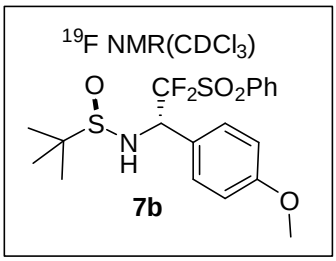


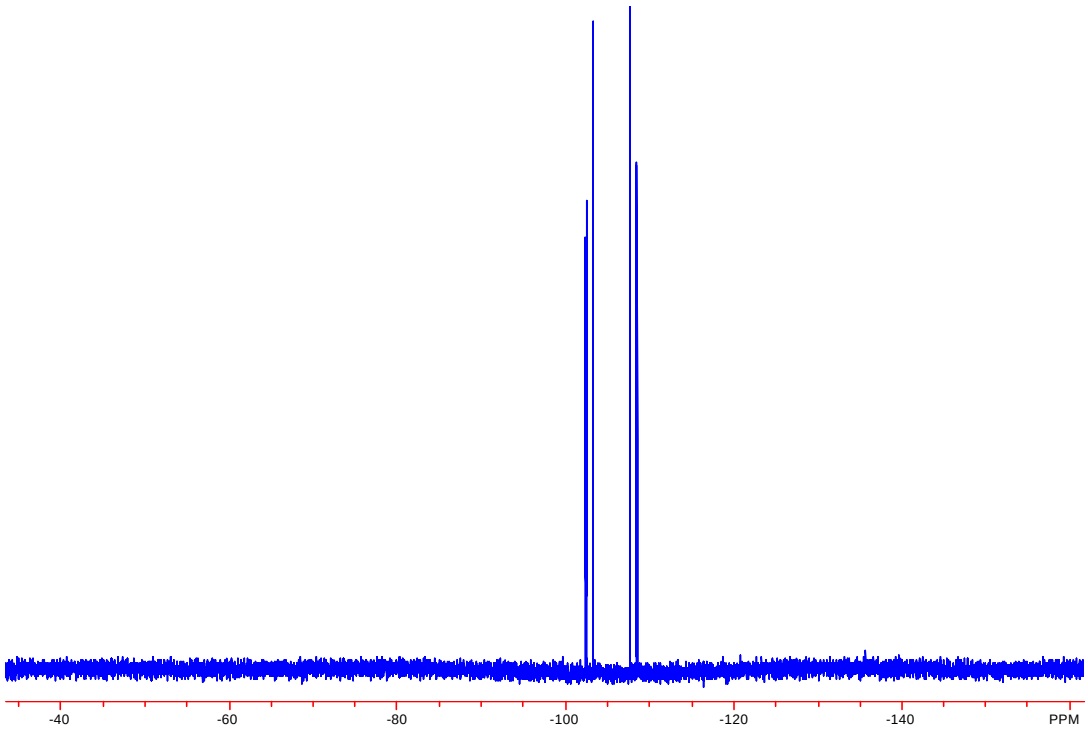
^{1}H NMR($CDCl_3$)



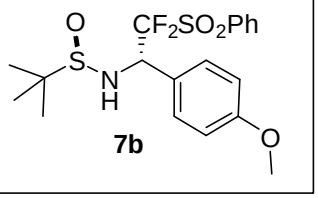
7b



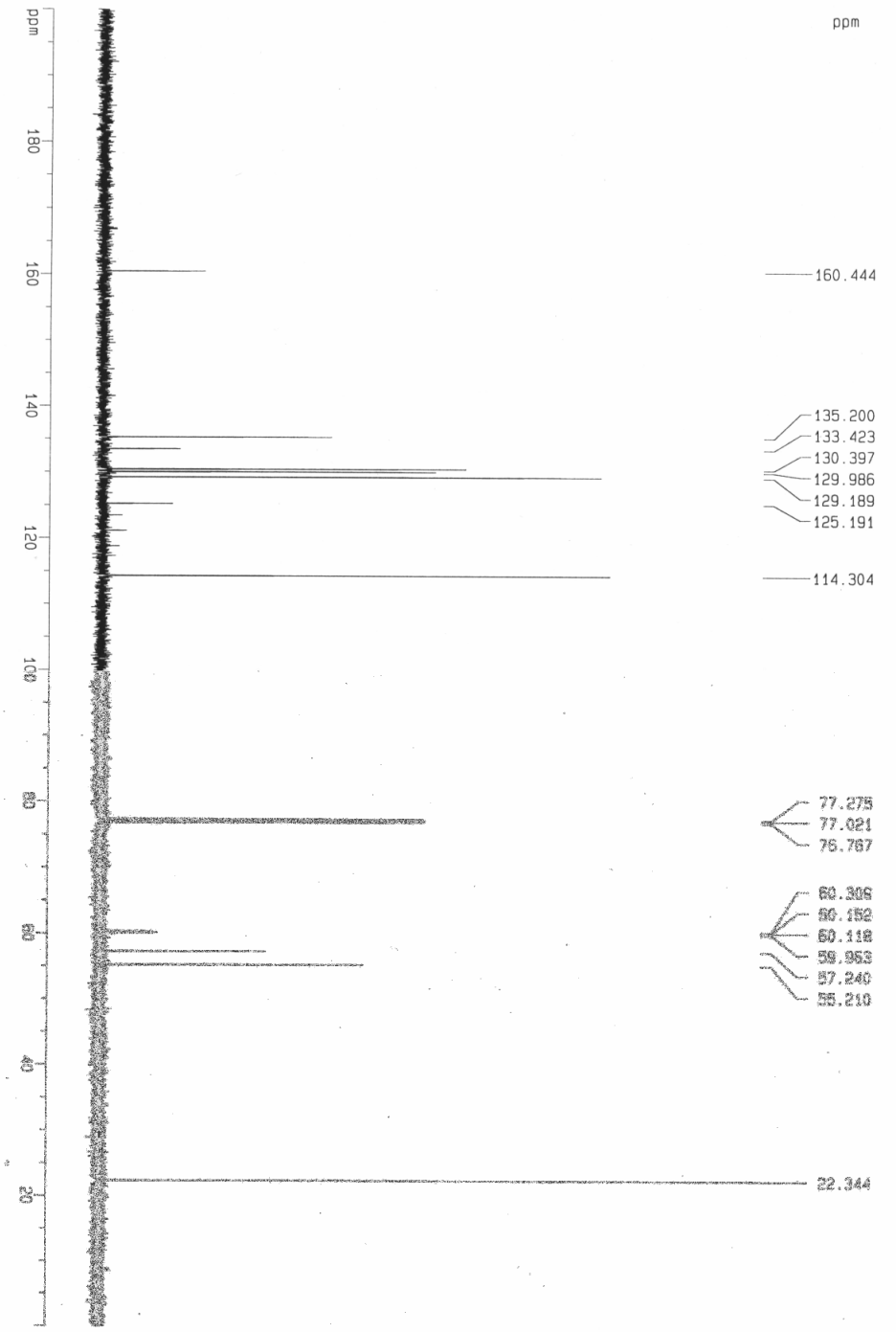

19F NMR(CDCl3)
O
S
N
H
CF2SO2Ph
O
7b


-40
-60
-80
-100
-120
-140
PPM

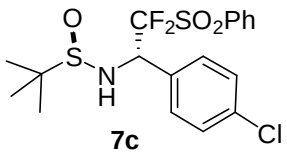
^{13}C NMR($CDCl_3$, 500M)



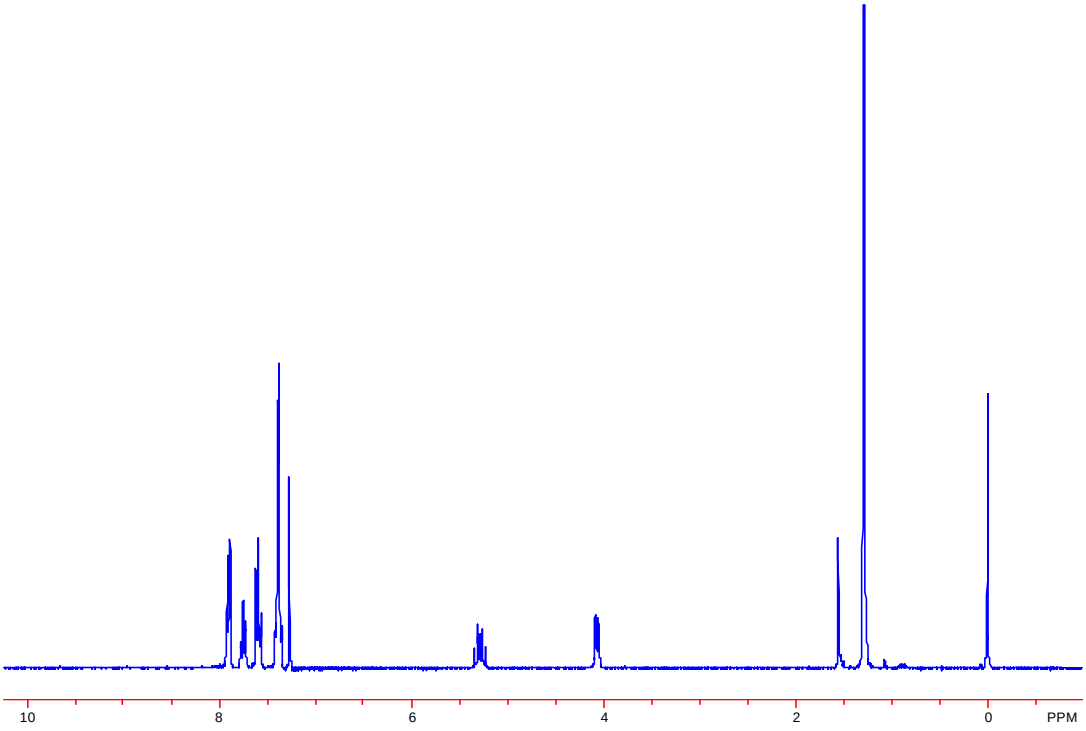
7b



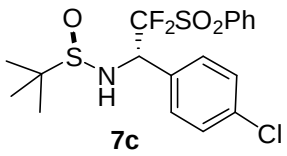
^{1}H NMR($CDCl_3$)



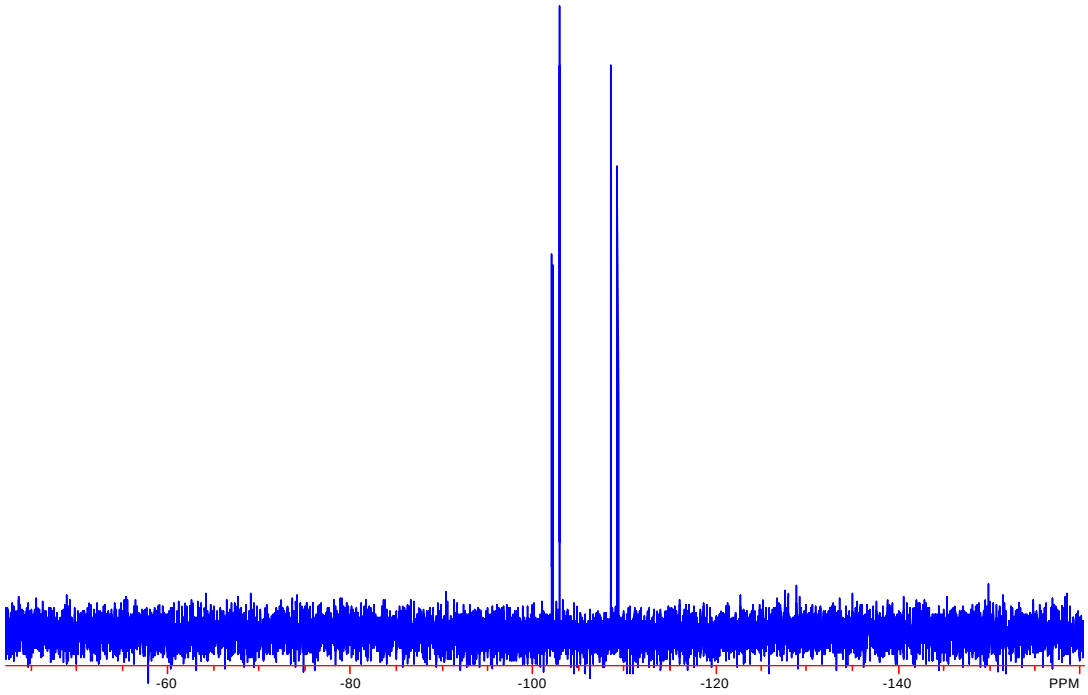
7c



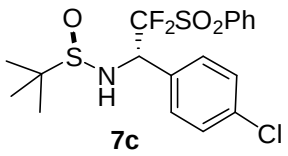
^{19}F NMR($CDCl_3$)



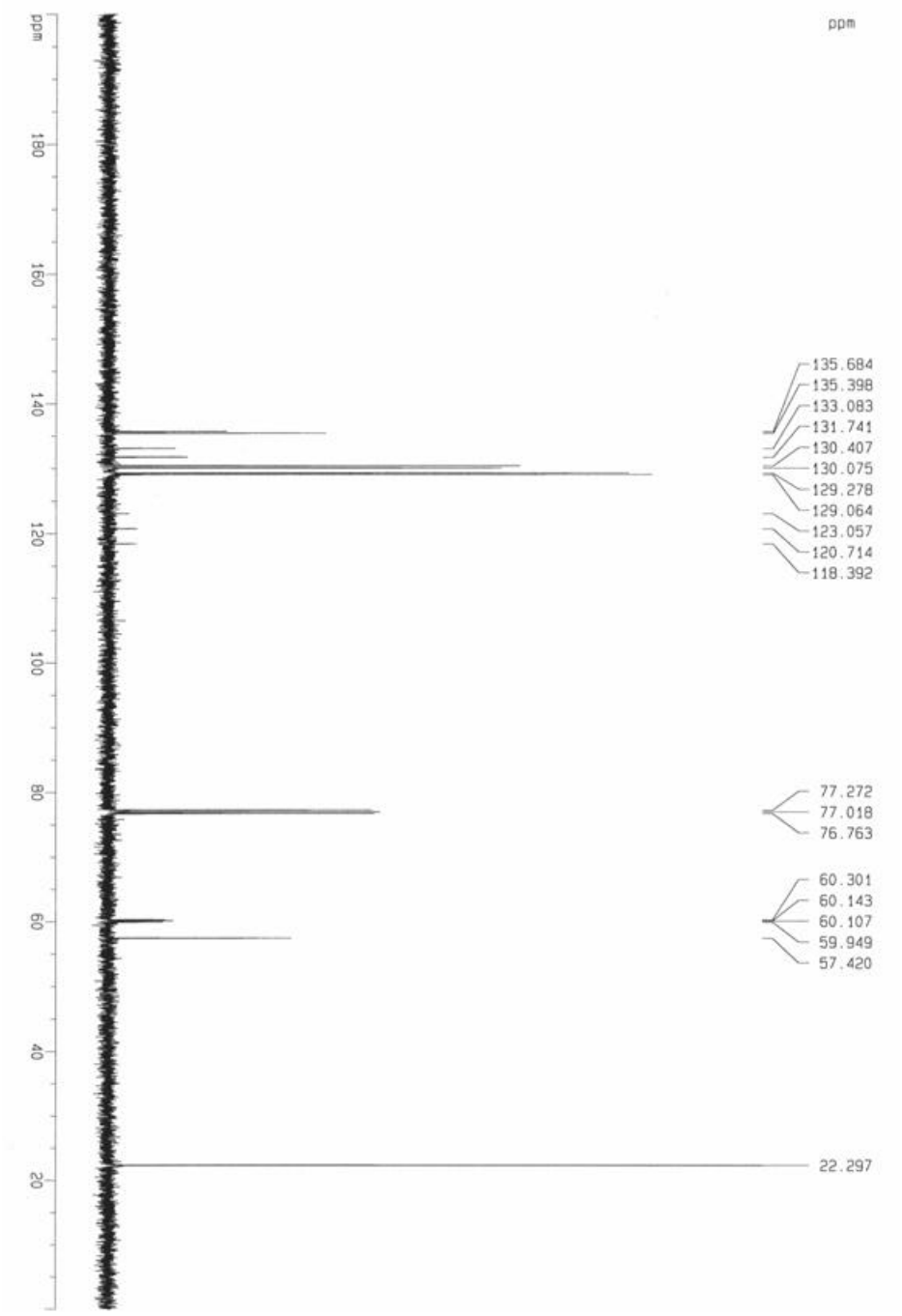
7c



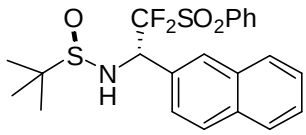
^{13}C NMR($CDCl_3$, 500M)



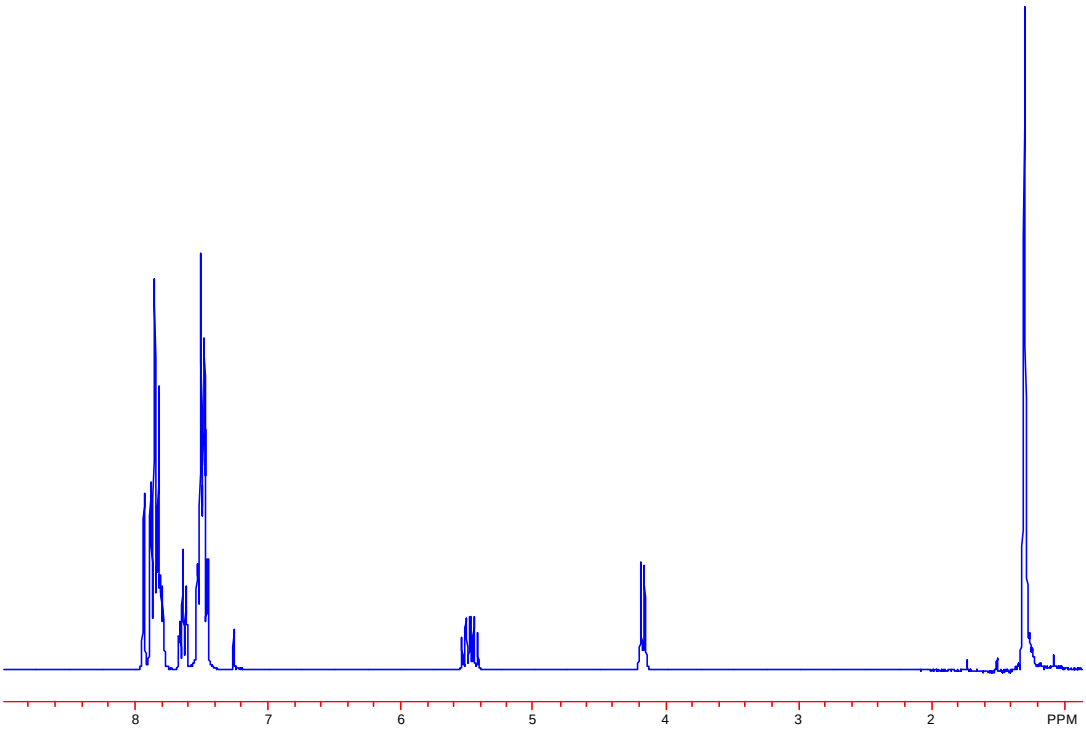
7c



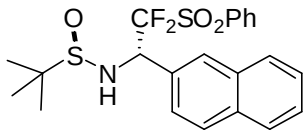
^{1}H NMR($CDCl_3$)



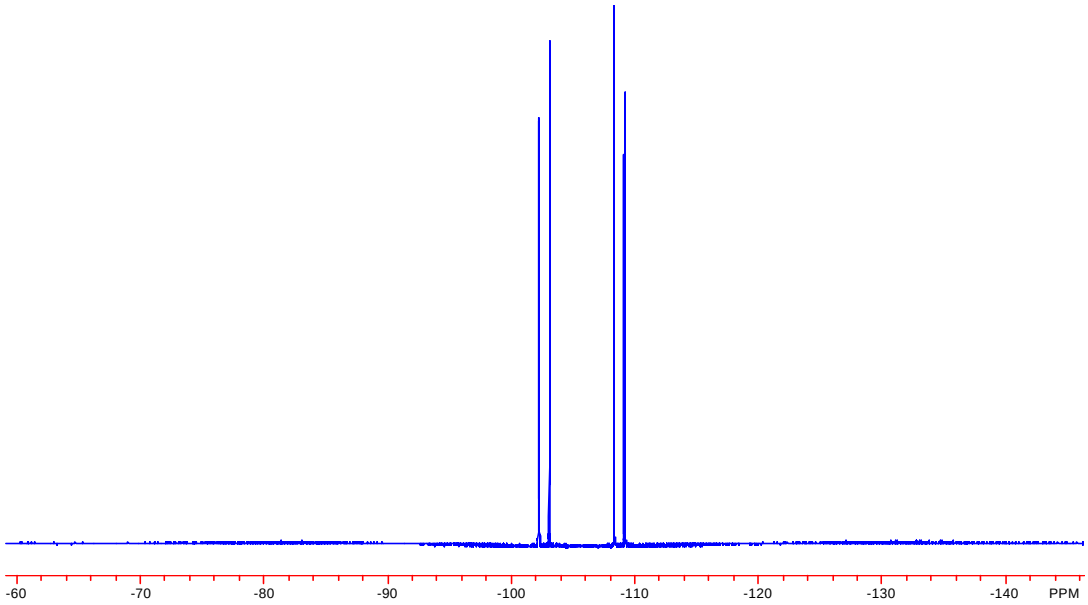
7d



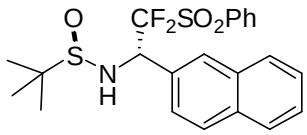
^{19}F NMR($CDCl_3$)



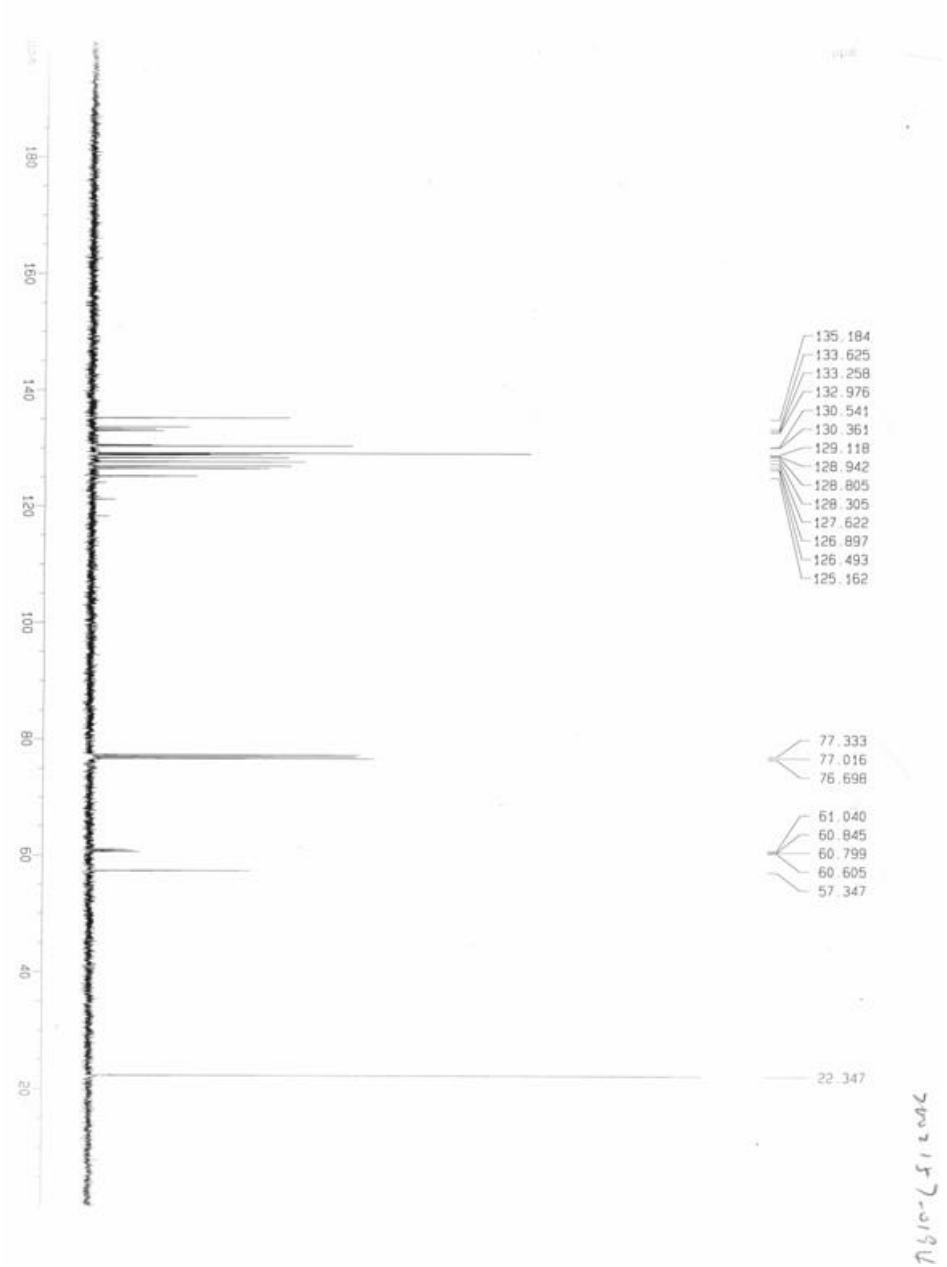
7d



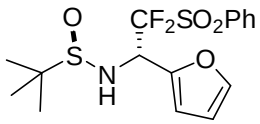
^{13}C NMR($CDCl_3$, 400M)



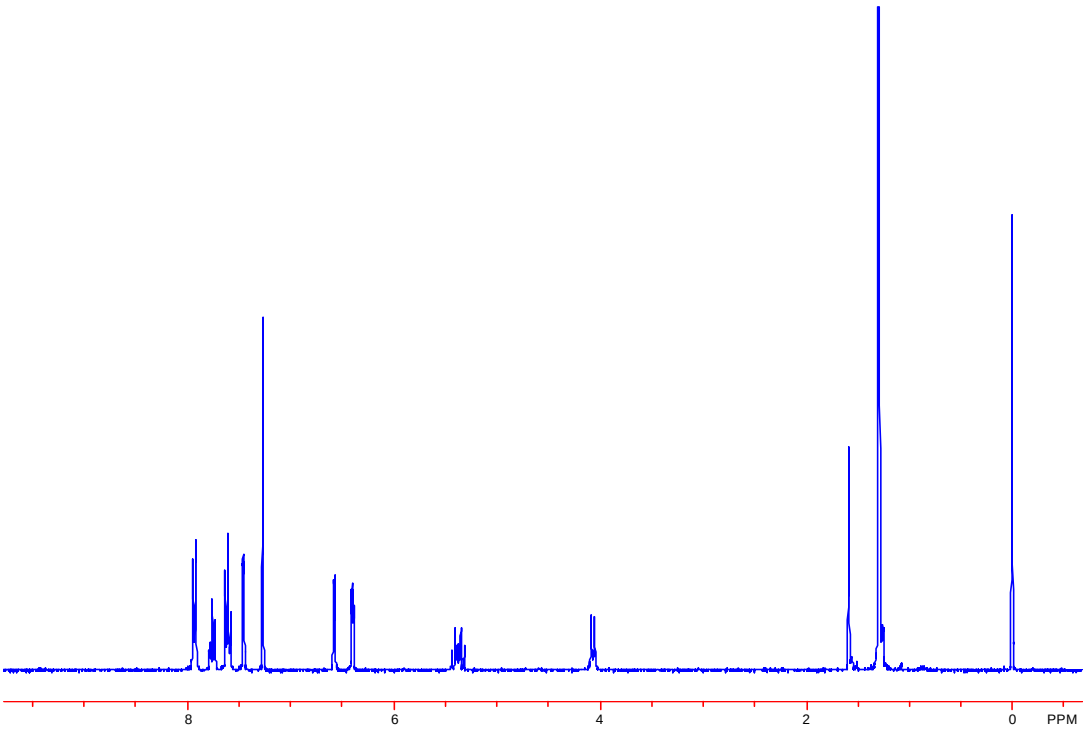
7d



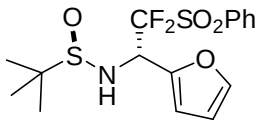
^{19}F NMR($CDCl_3$)



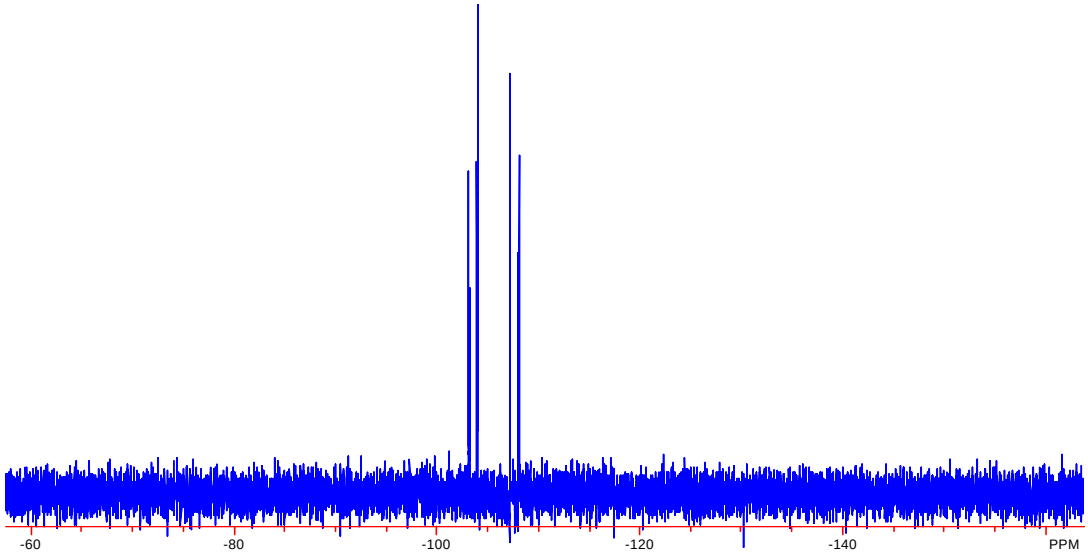
7e



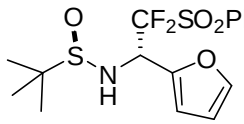
^{19}F NMR($CDCl_3$)



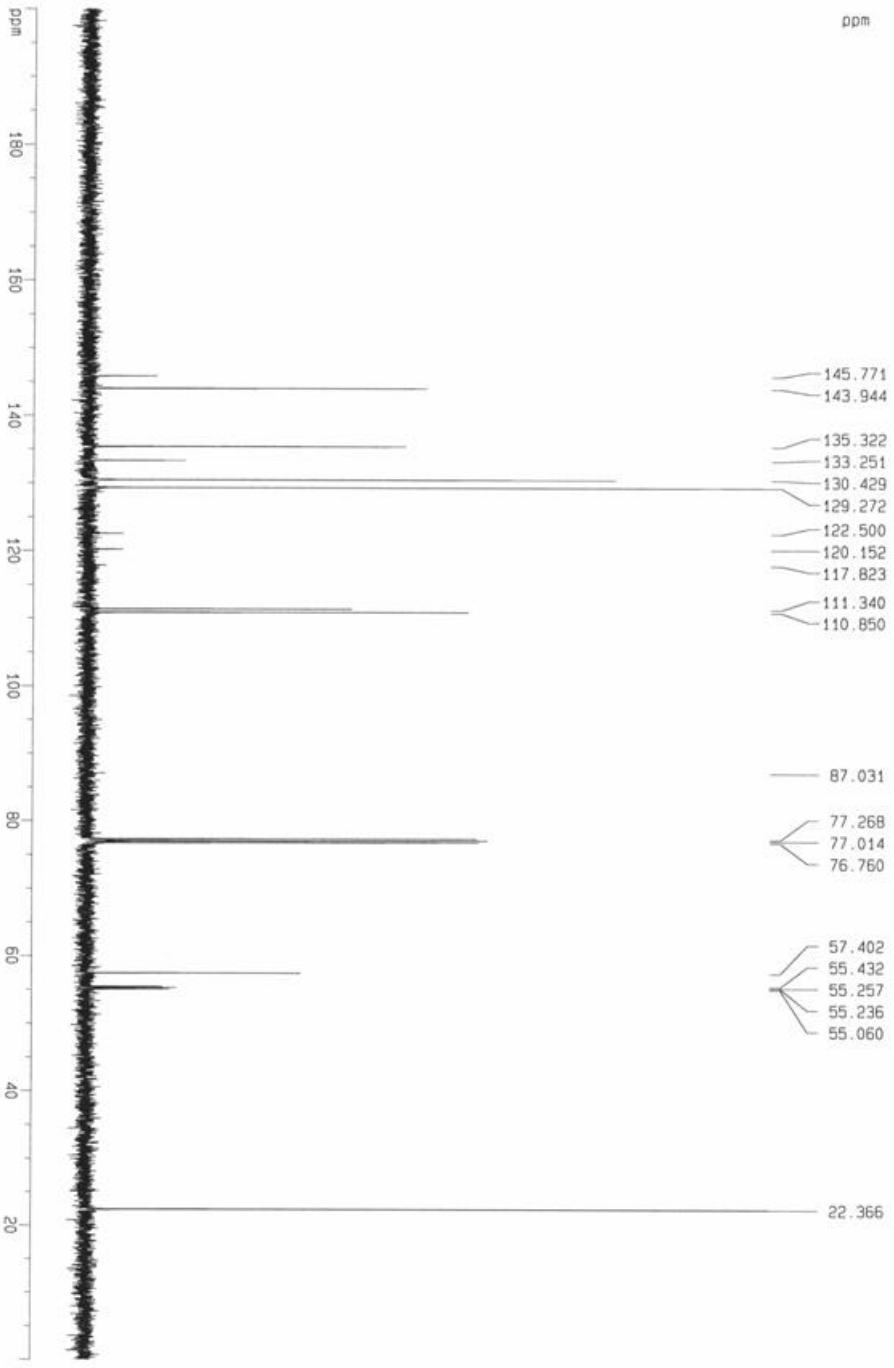
7e



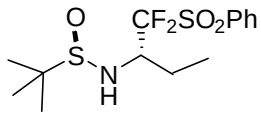
^{13}C NMR($CDCl_3$, 400M)



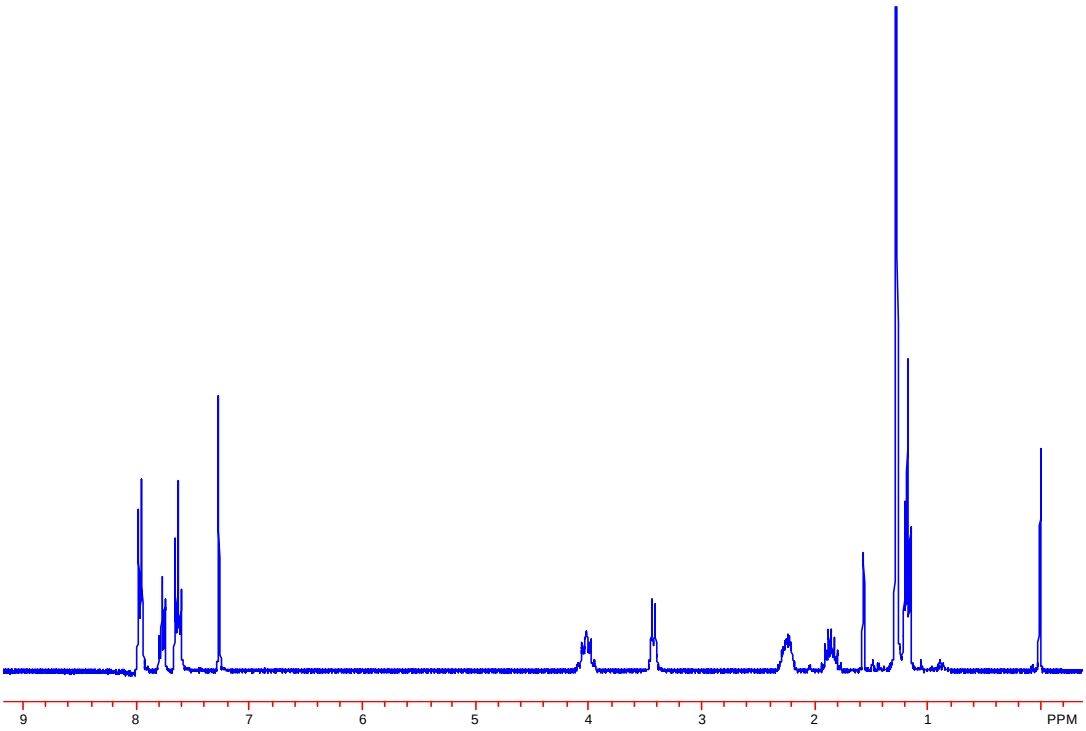
7e



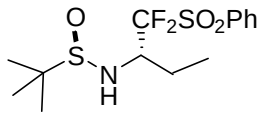
^{1}H NMR($CDCl_3$)



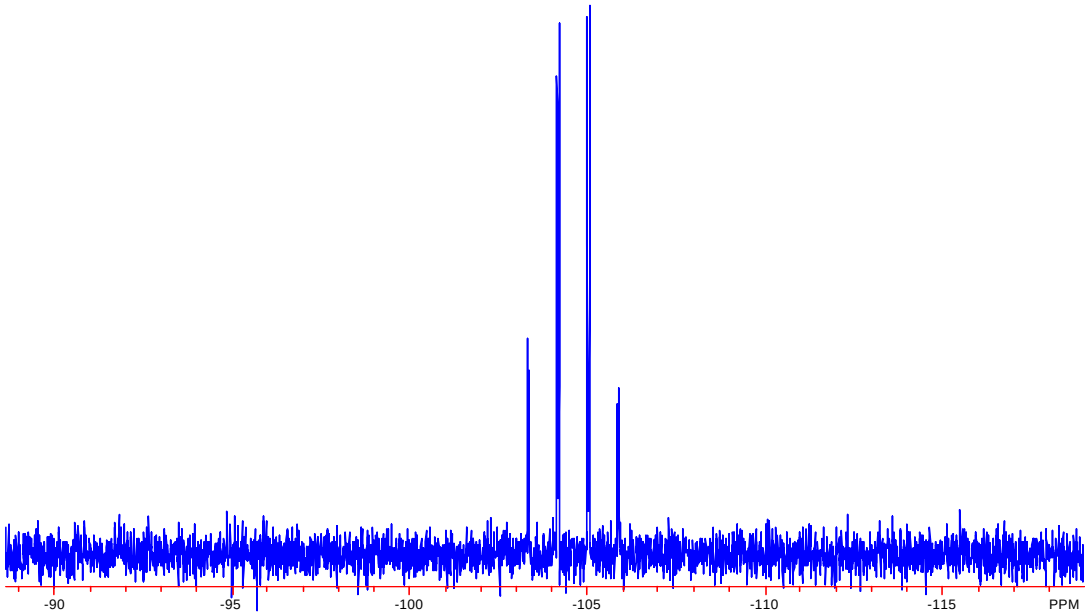
7f



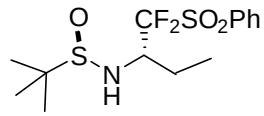
^{19}F NMR($CDCl_3$)



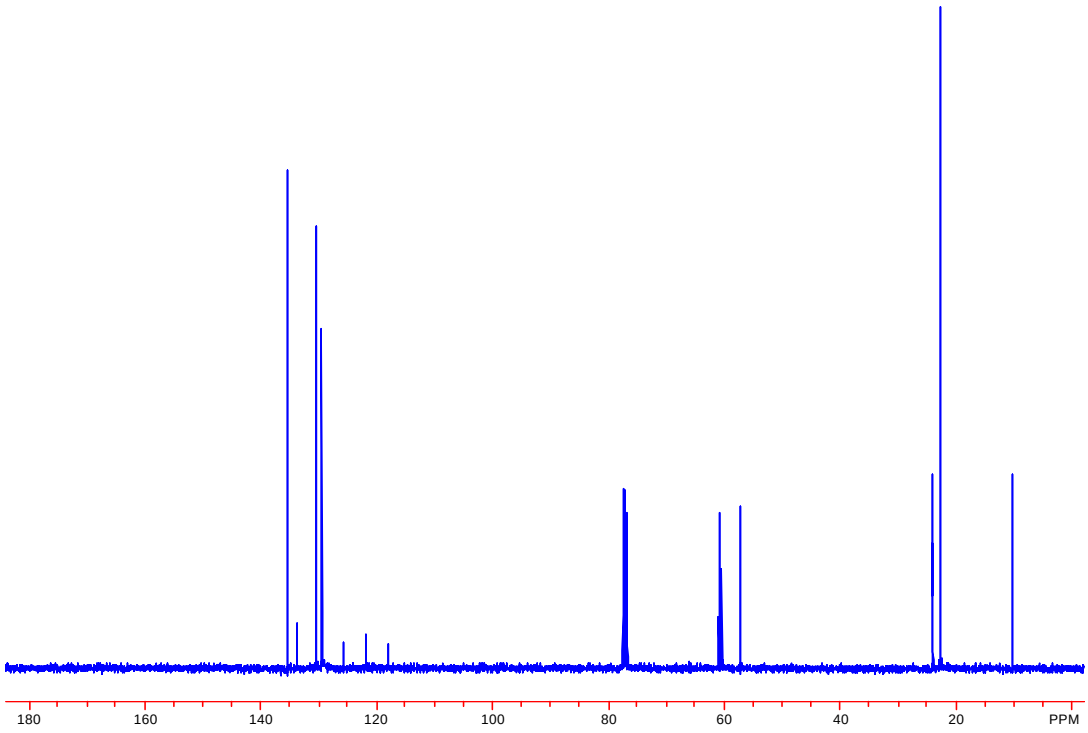
7f



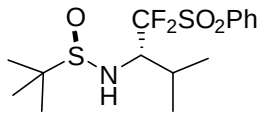
^{13}C NMR($CDCl_3$, 300M)



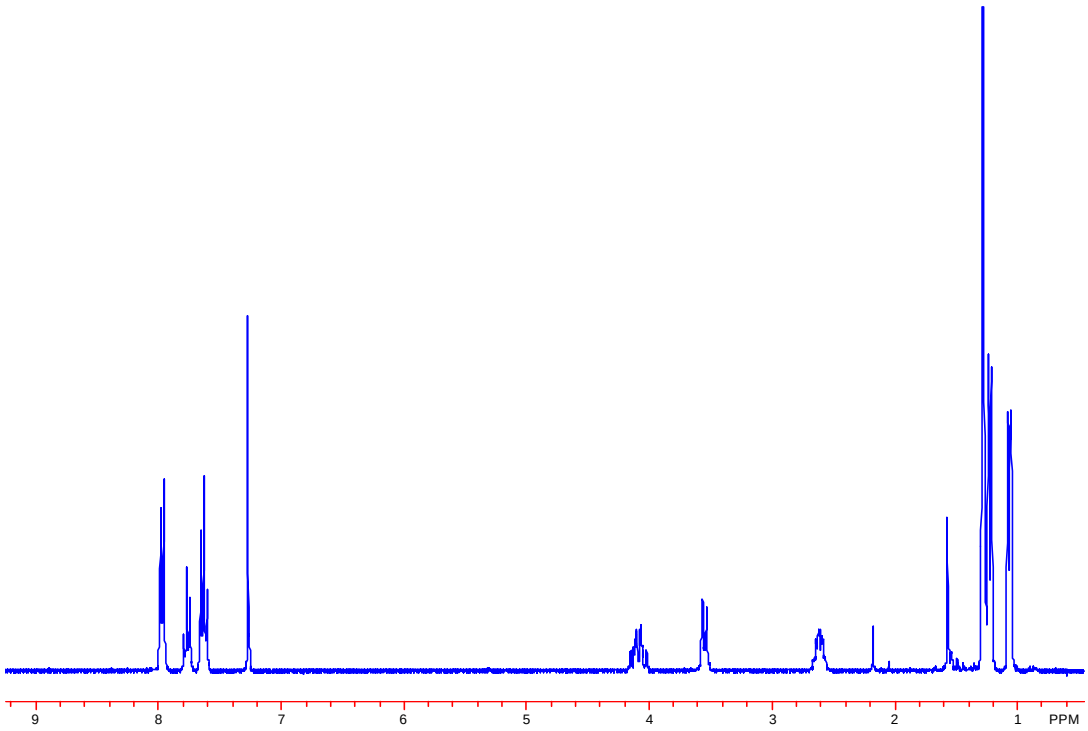
7f



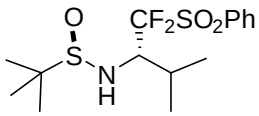
^{1}H NMR($CDCl_3$)



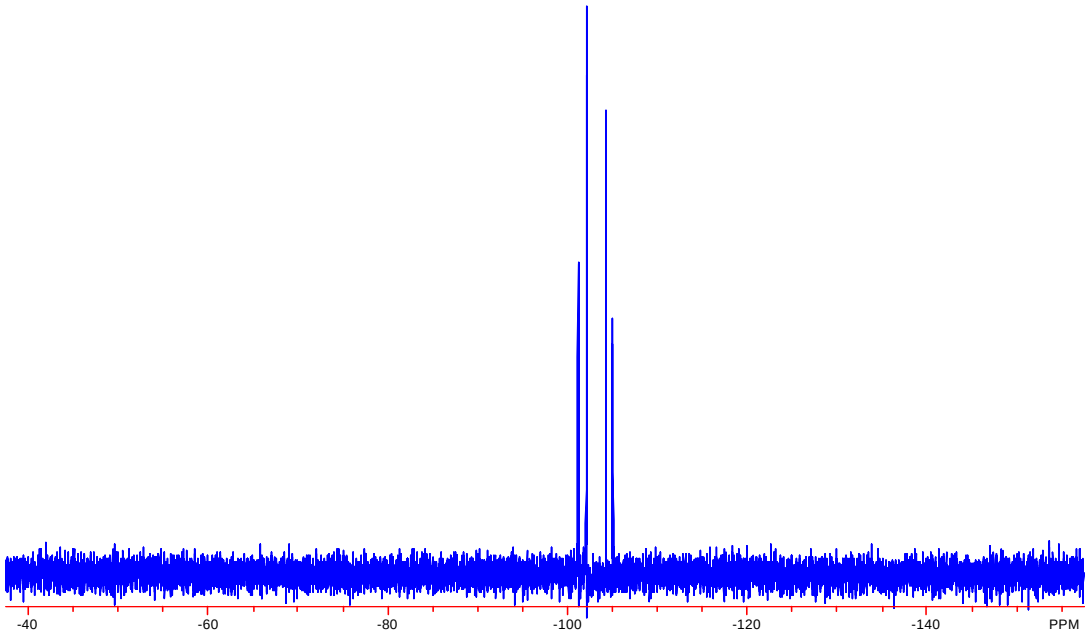
7g



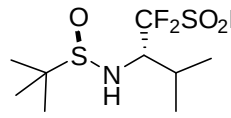
^{19}F NMR($CDCl_3$)



7g



^{13}C(NMR($CDCl_3$, 500M)



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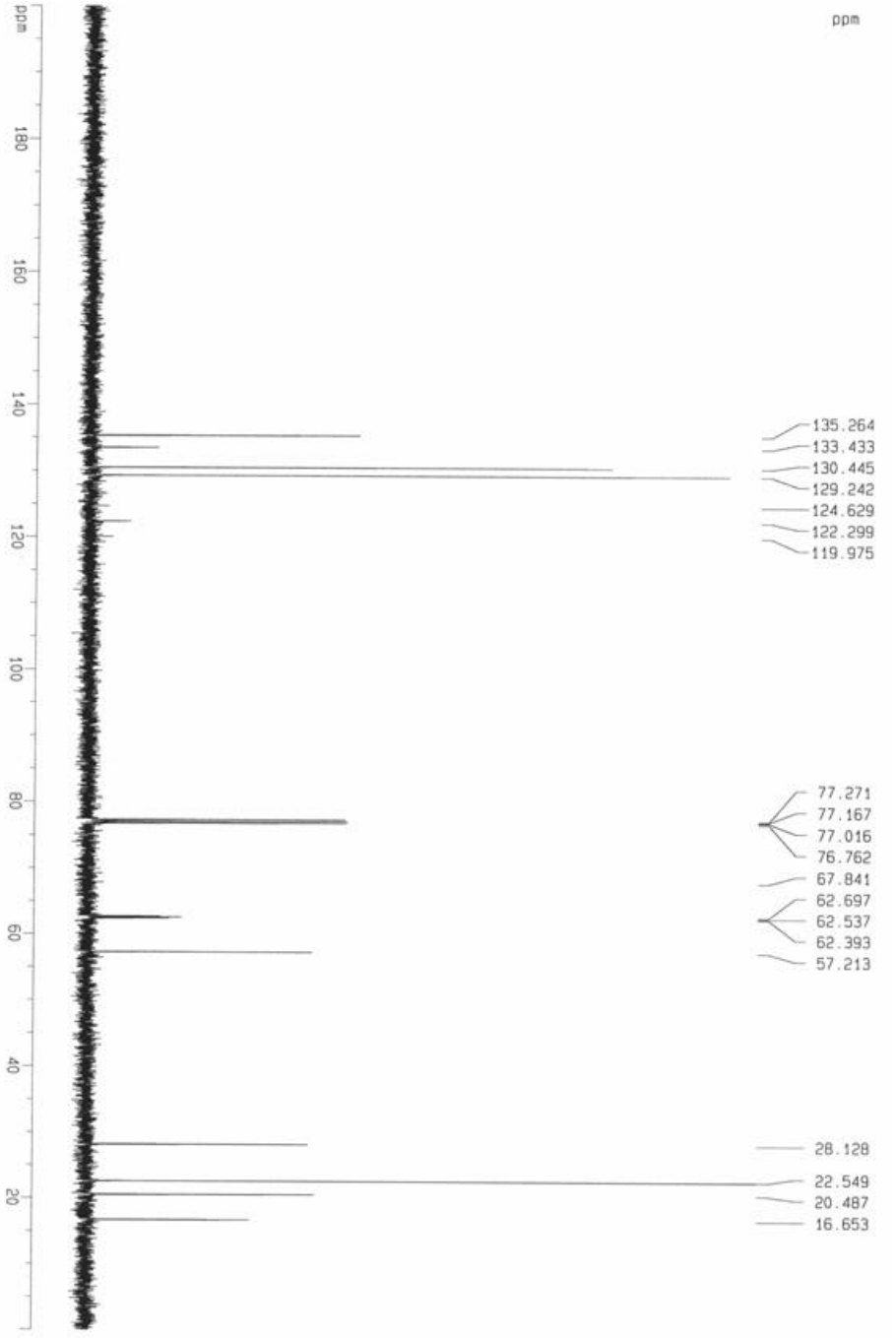
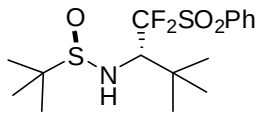


^{1}H NMR ($CDCl_3$)



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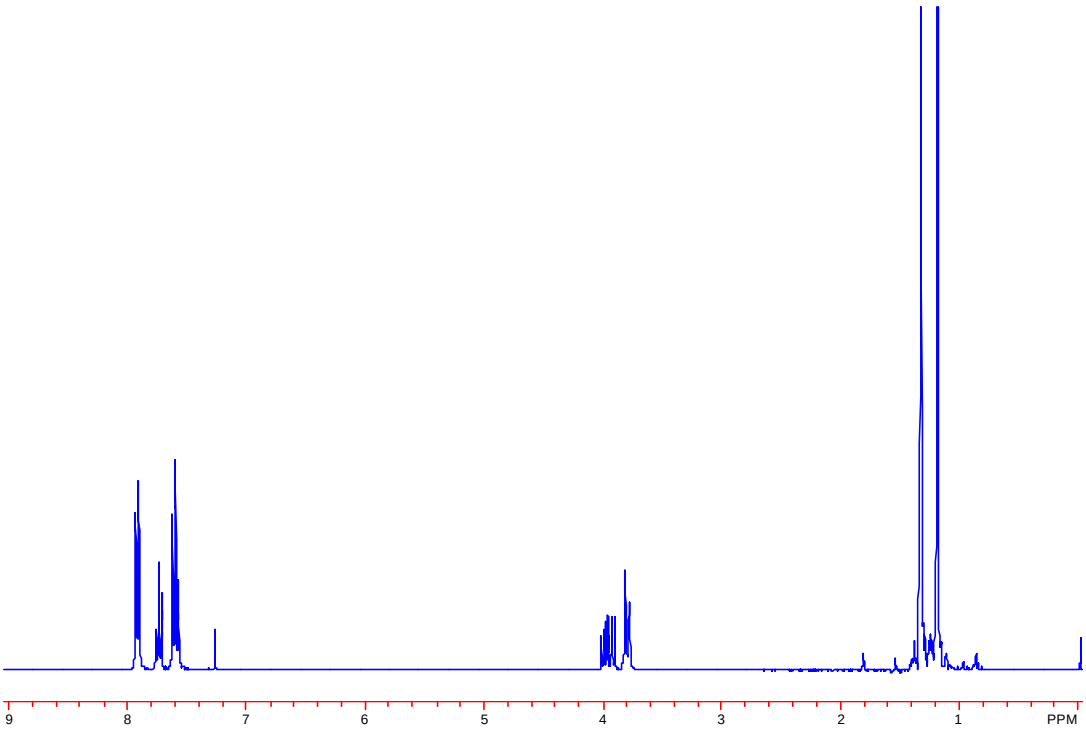
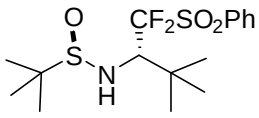


^{19}F NMR($CDCl_3$)



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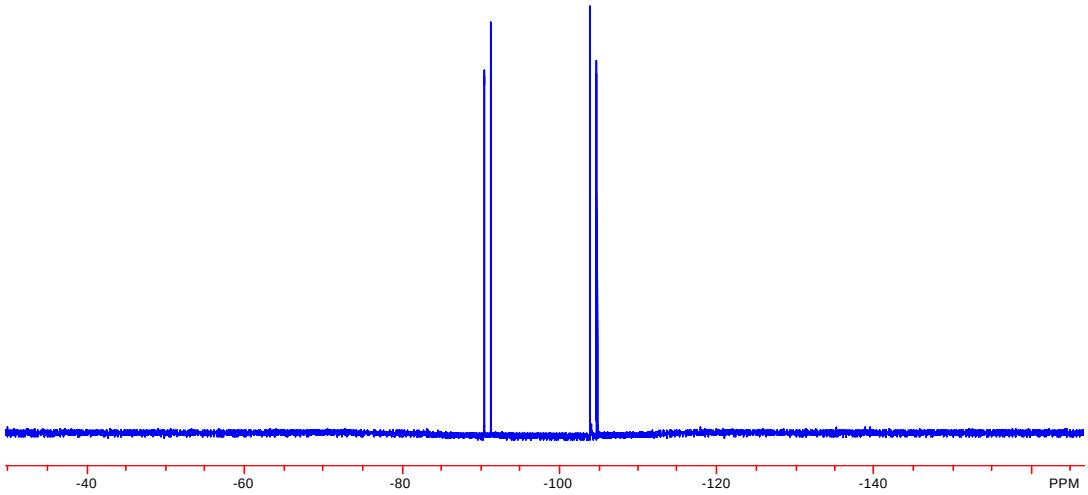
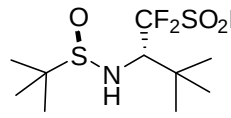


^{13}C NMR($CDCl_3$, 500M)



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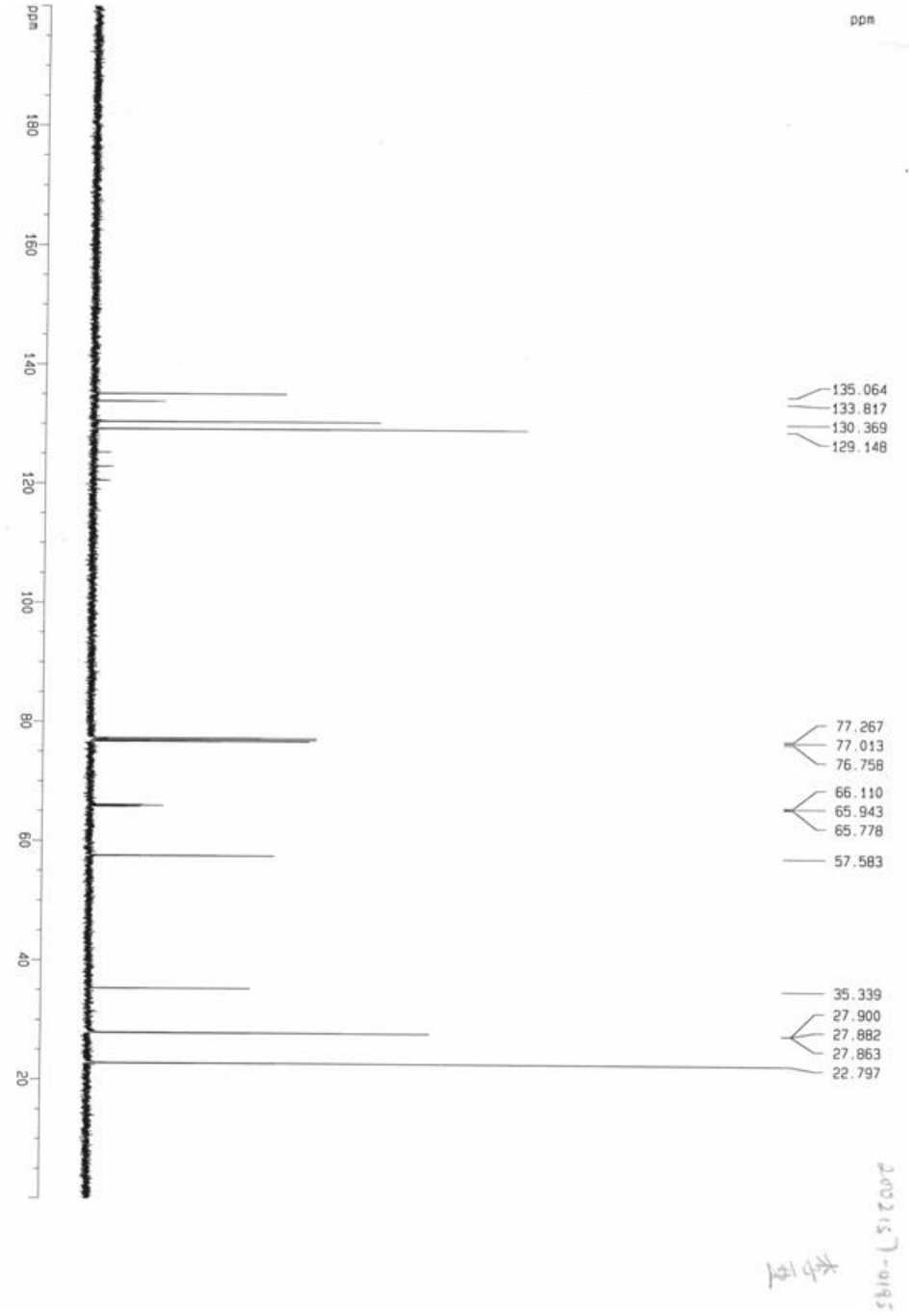
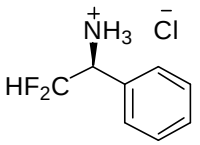


^{1}H NMR (CD_3OD)



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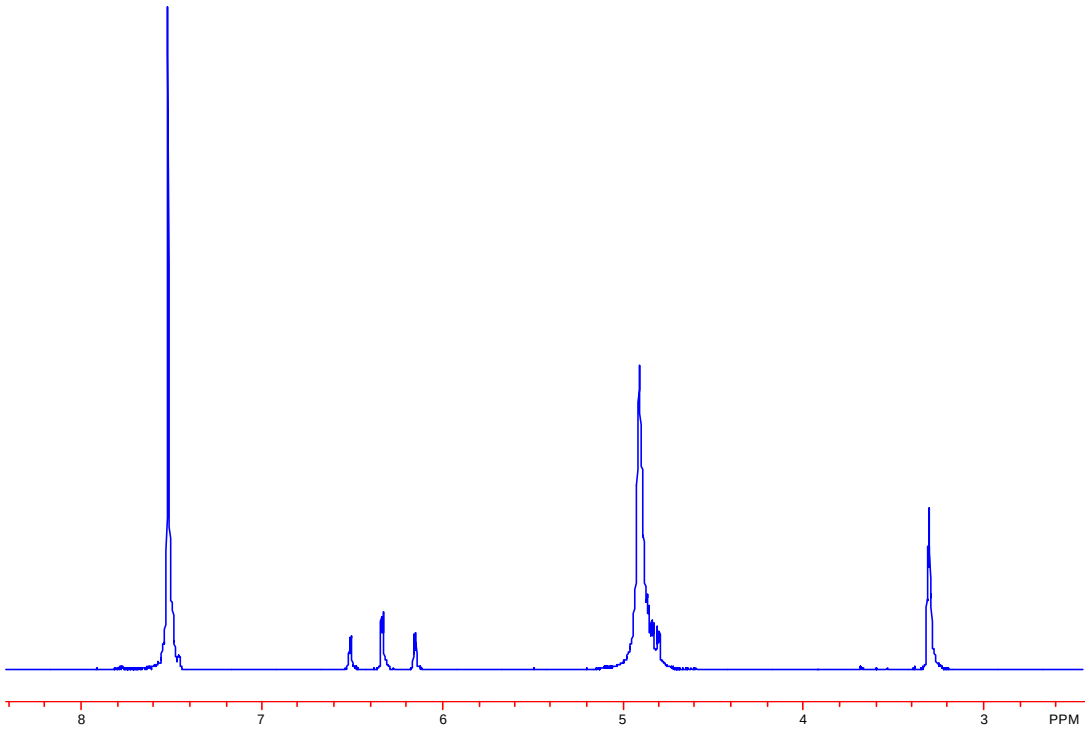
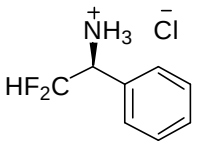


^{19}F NMR (CD_3OD)



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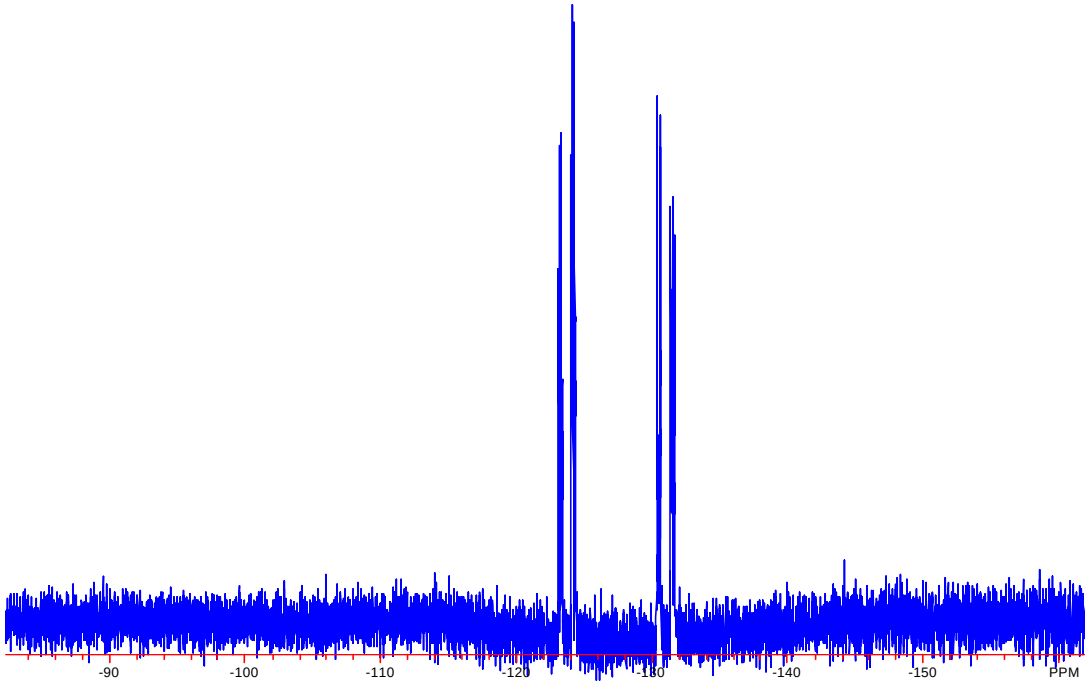
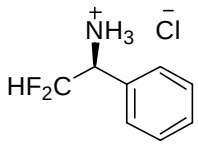


^{13}C NMR (CD_3OD)



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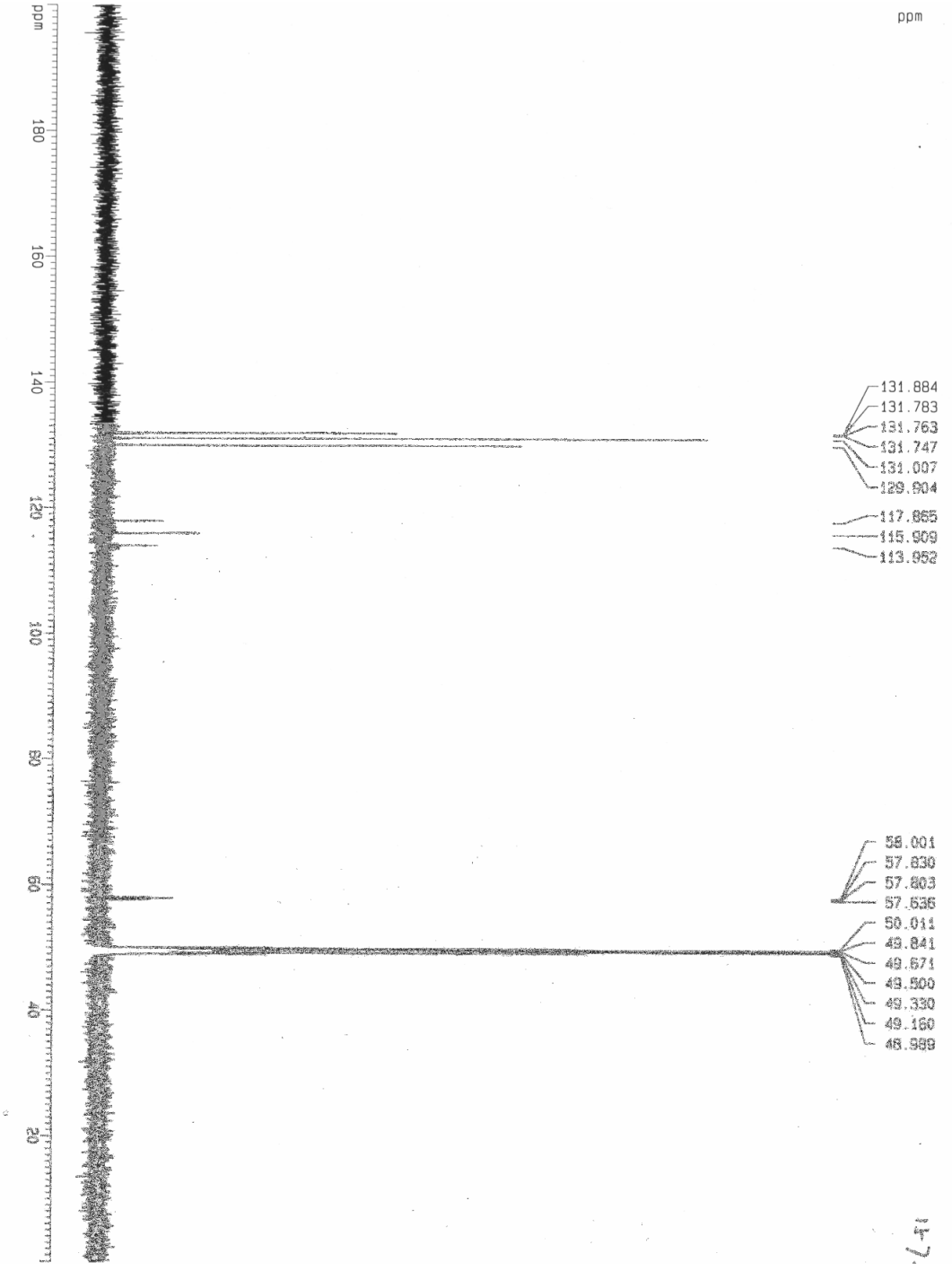
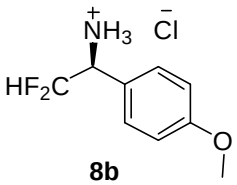


^{1}H NMR (CD_3OD)



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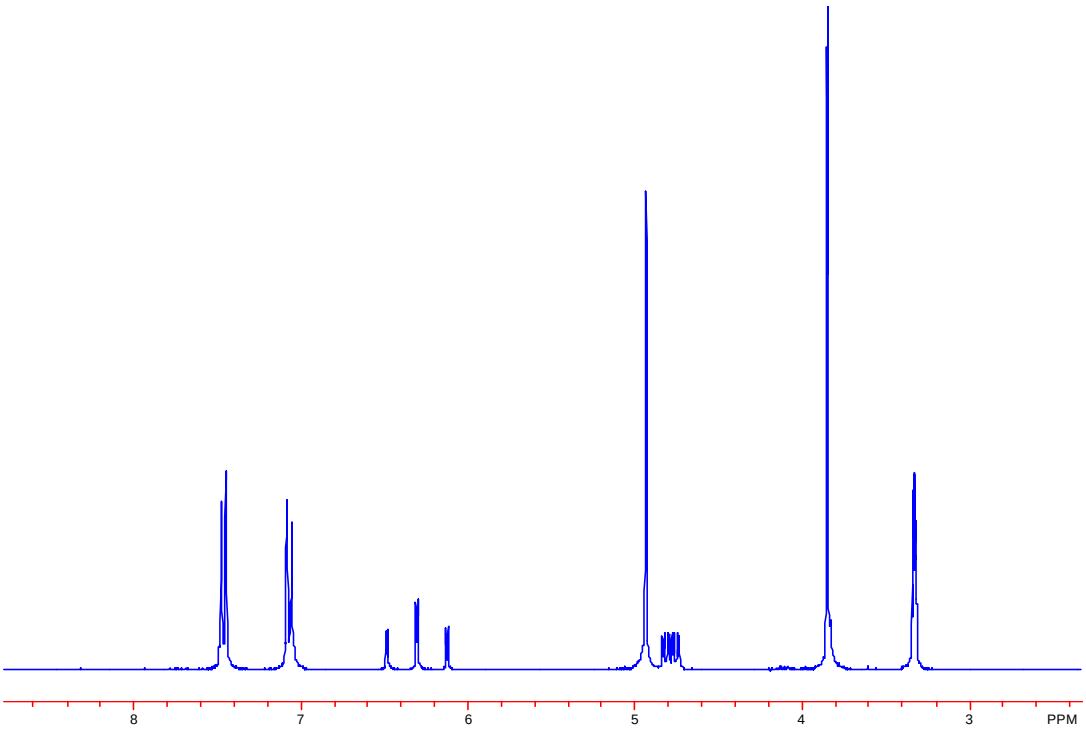
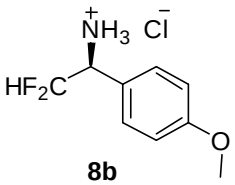


^{19}F NMR (CD_3OD)



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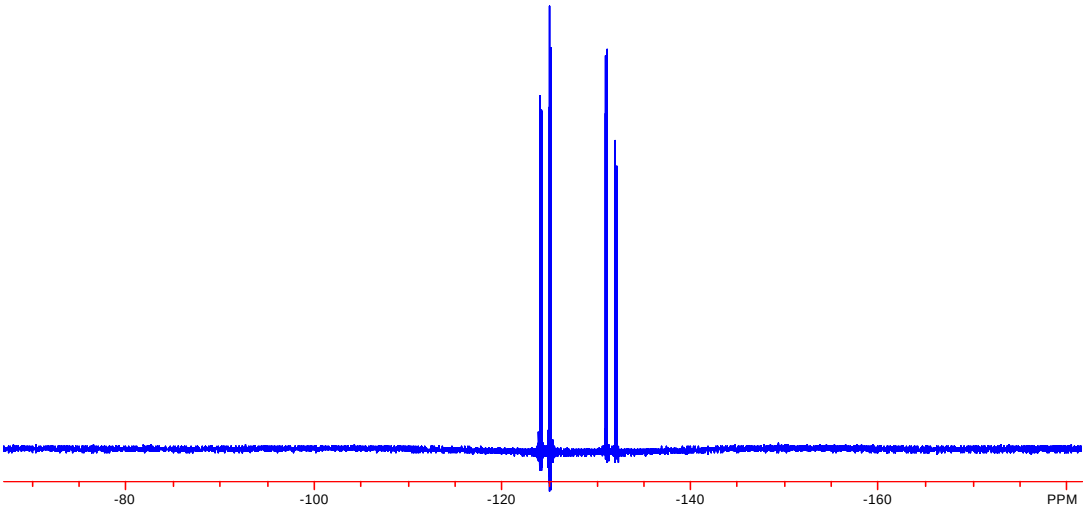
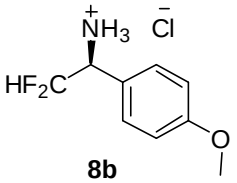


^{13}C NMR (CD_3OD, 400M)



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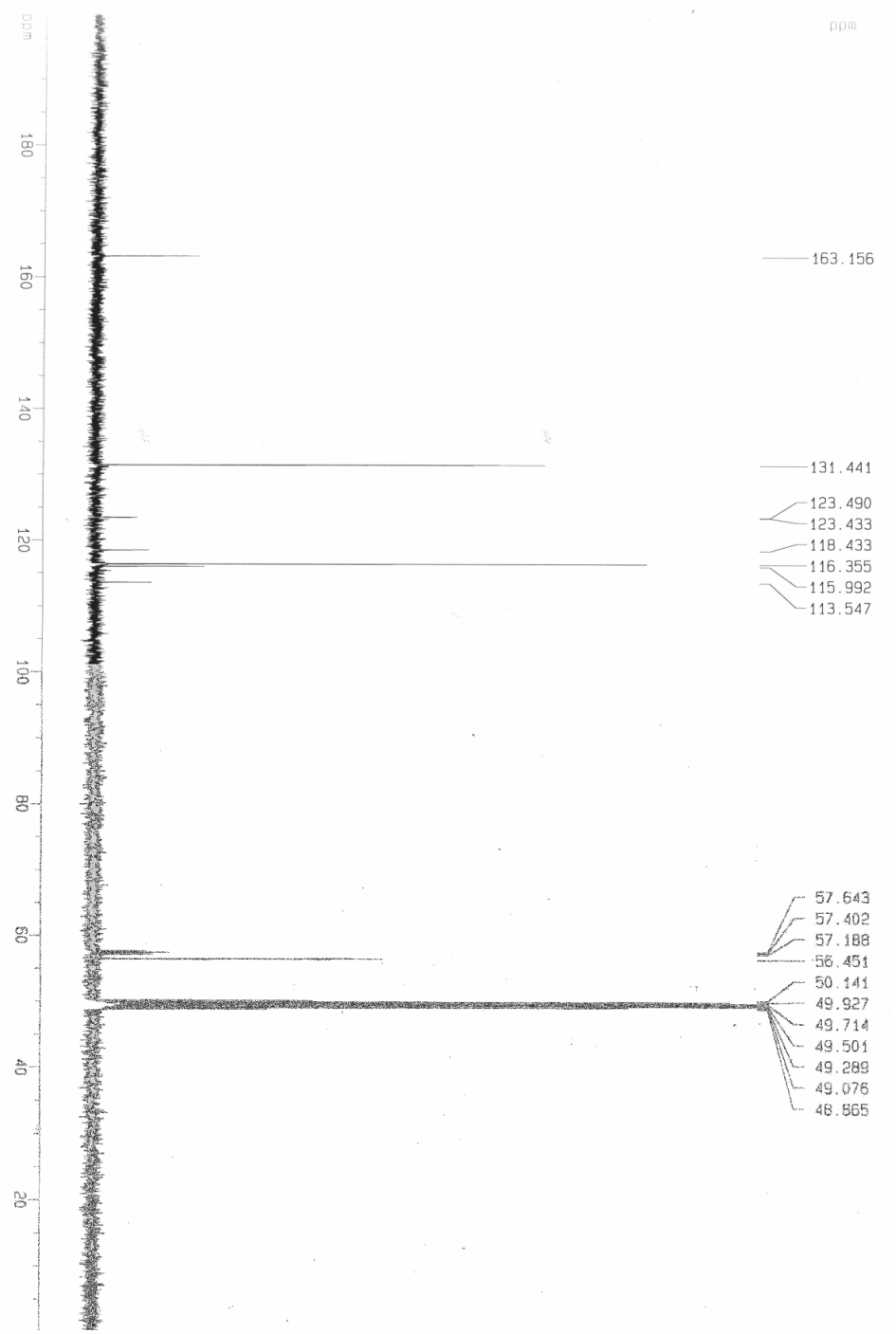
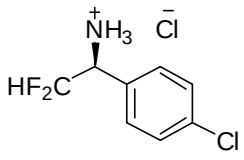


^{1}H NMR (CD_3OD)



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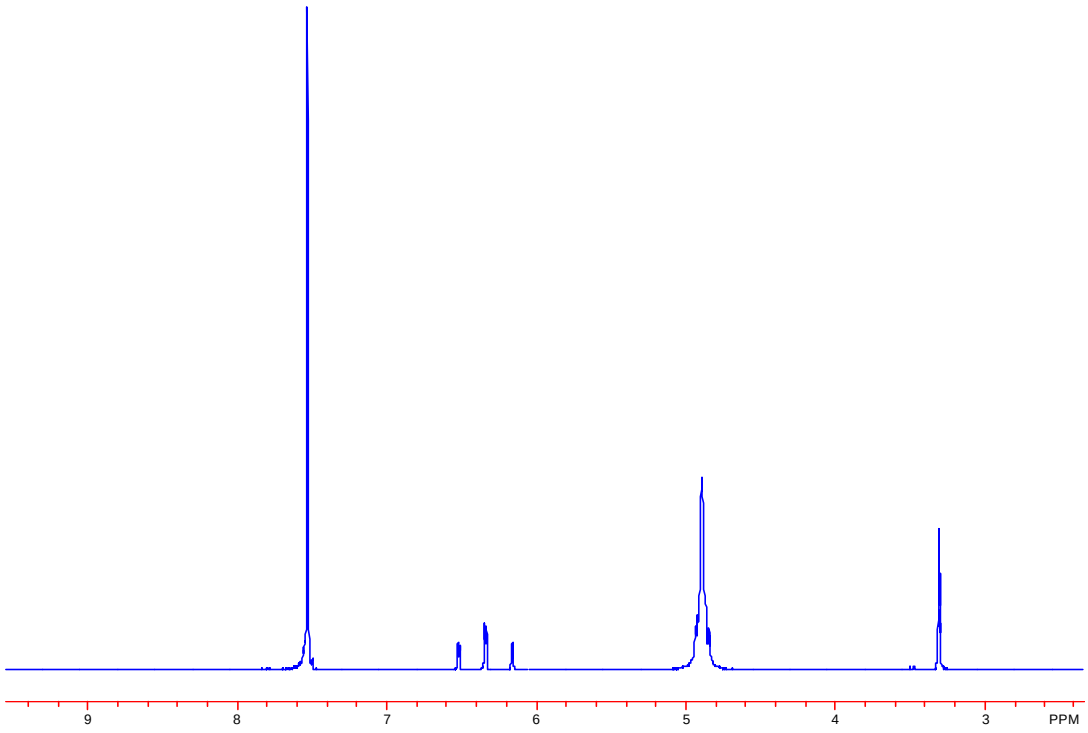
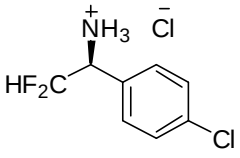


^{19}F NMR (CD_3OD)



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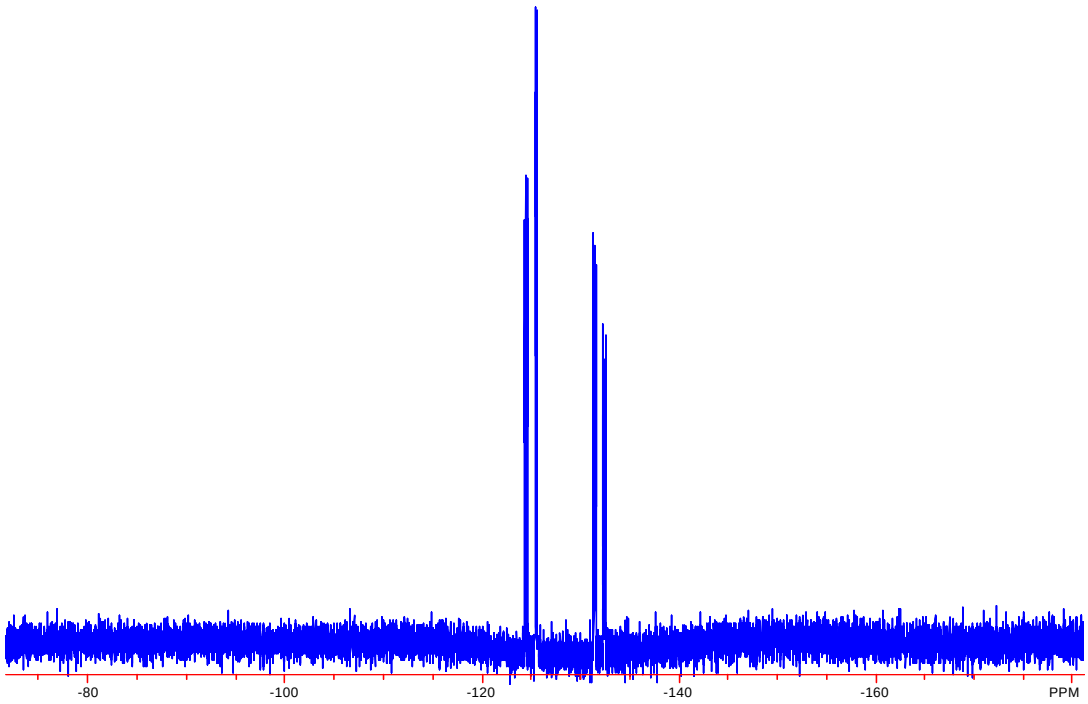
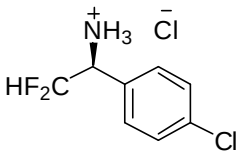


^{13}C NMR (CD_3OD)



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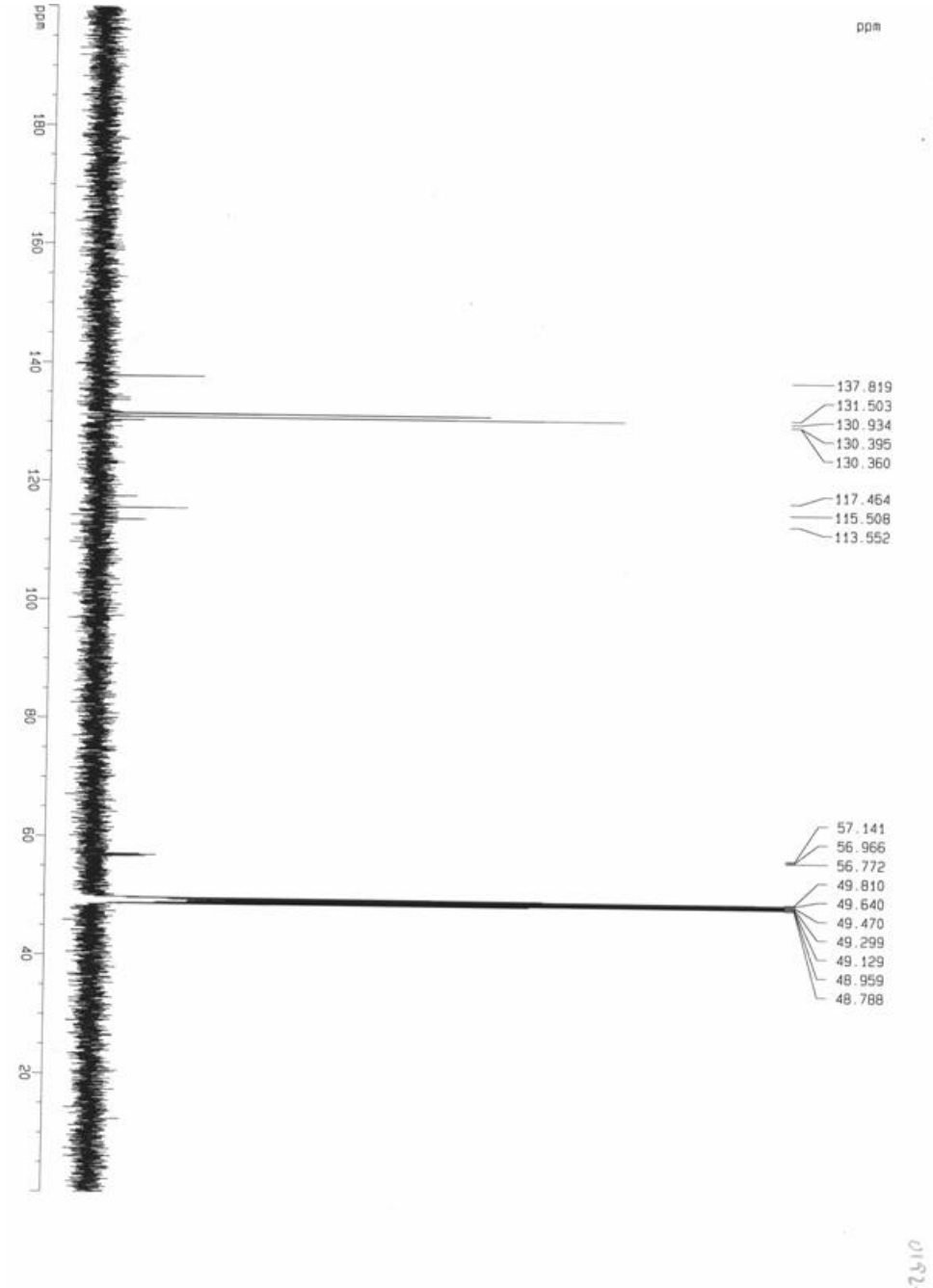
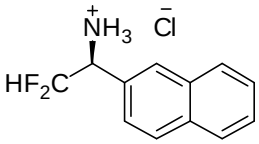


^{1}H NMR (CD_3OD)



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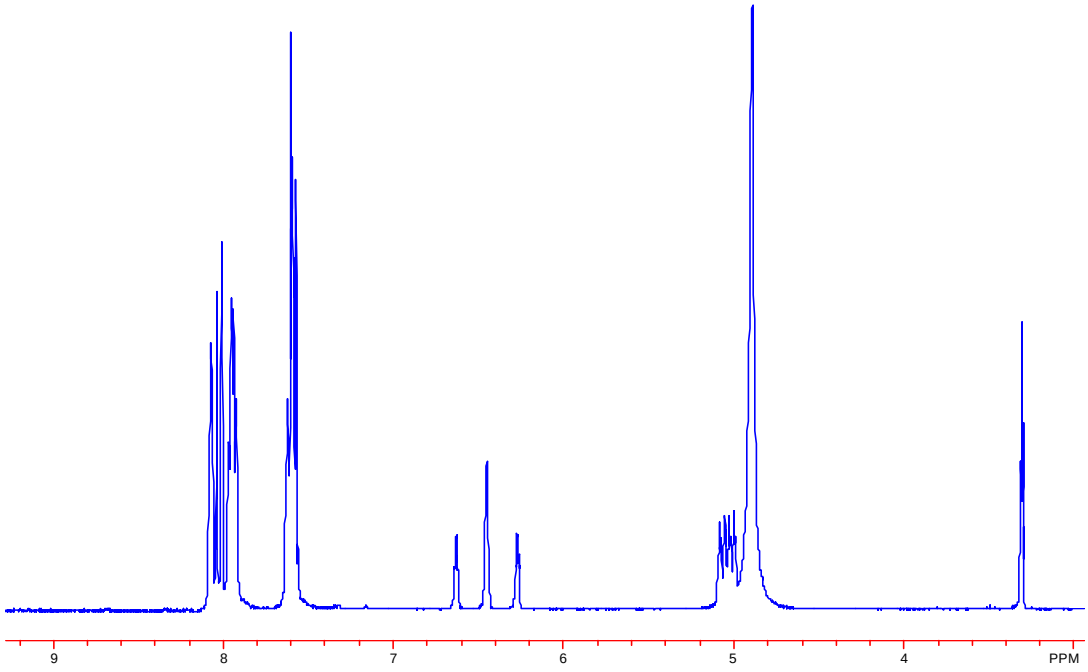
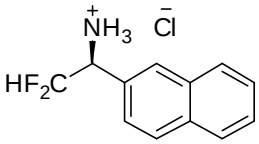


^{19}F NMR (CD_3OD)



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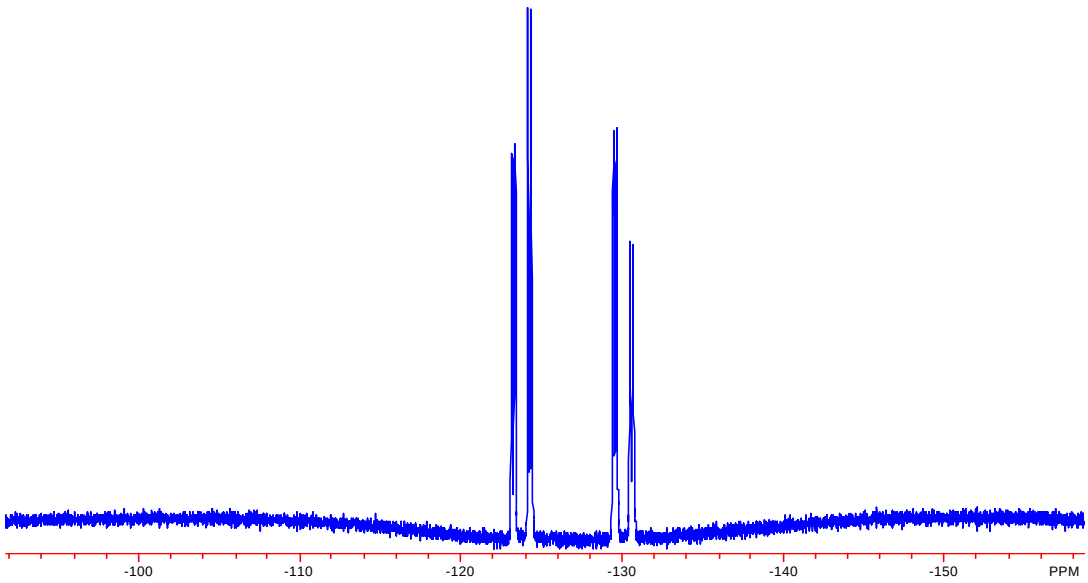
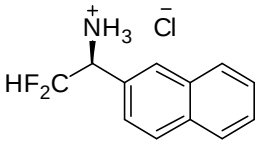


^{13}C NMR (CD_3OD)



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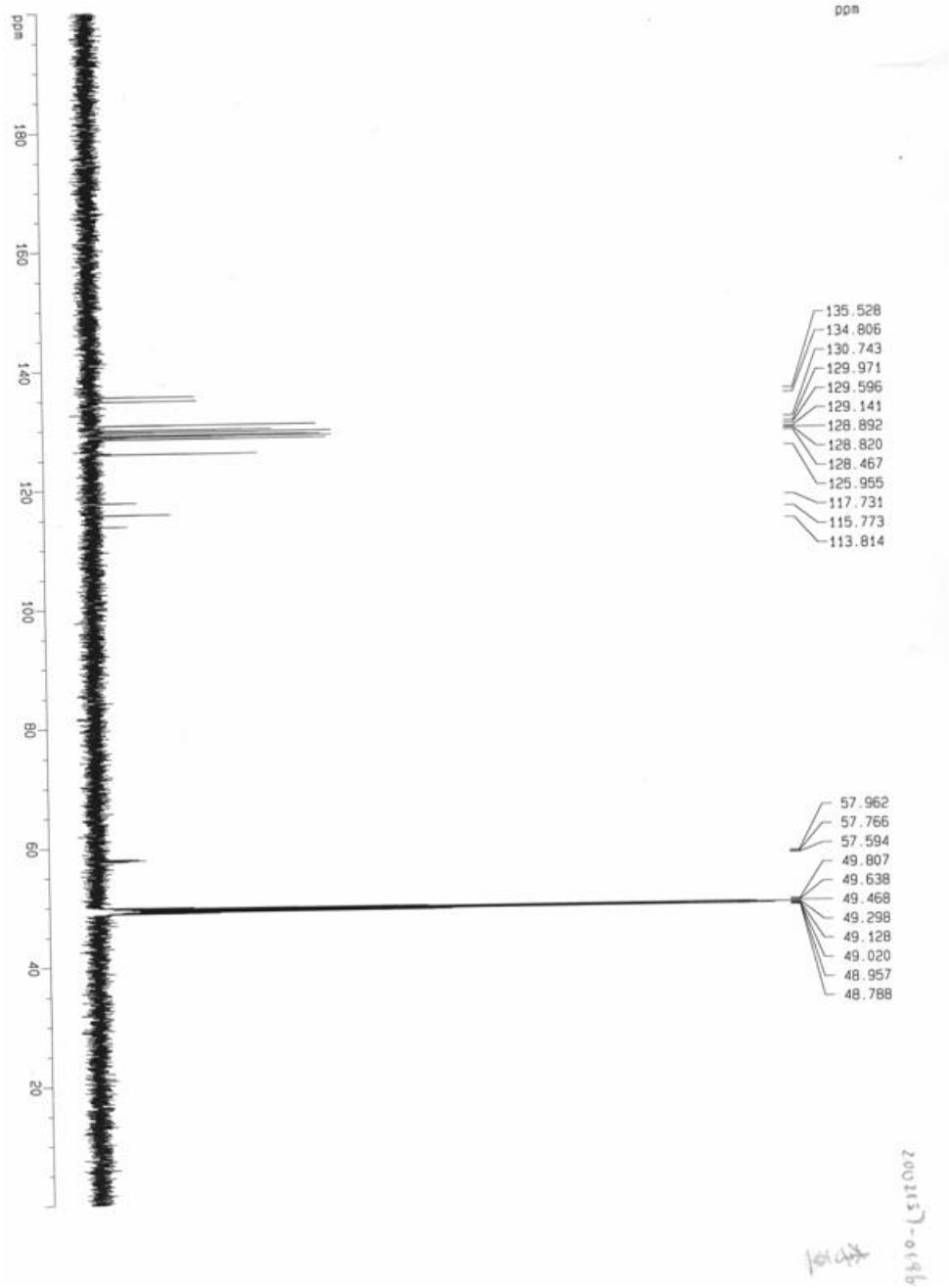
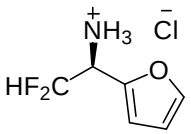


^{1}H NMR (CD_3OD)



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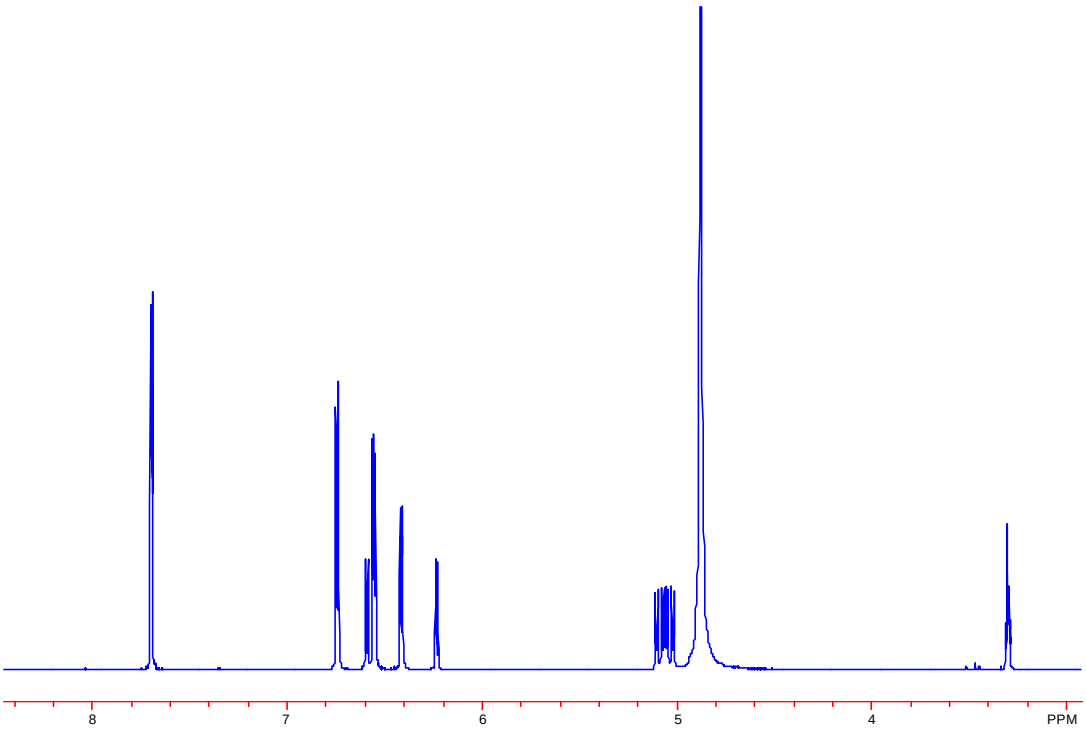
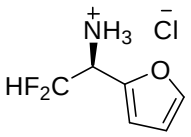


^{19}F NMR (CD_3OD)



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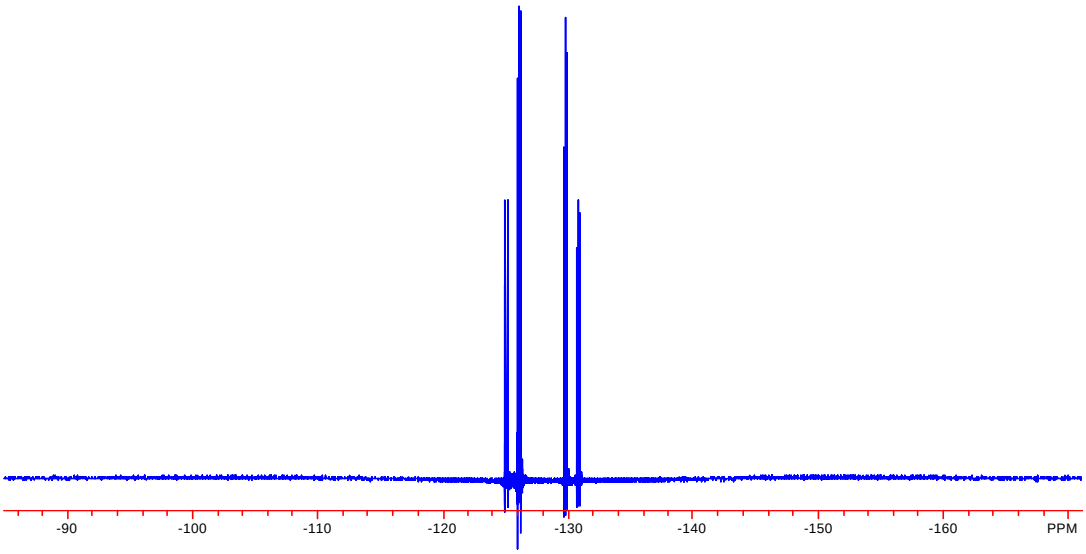
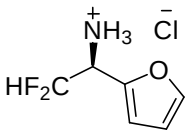


^{13}C NMR (CD_3OD)



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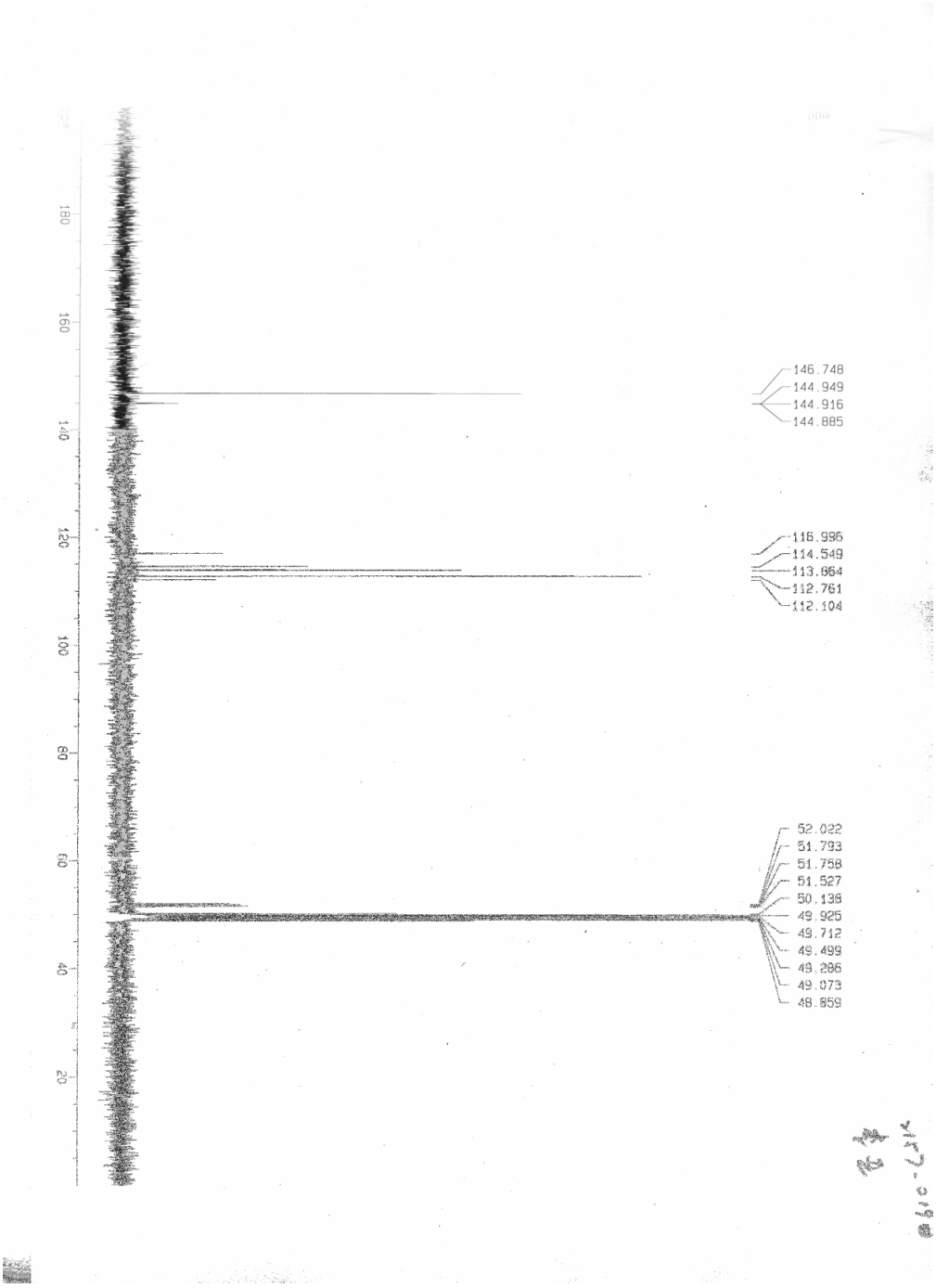
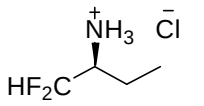


^{1}H NMR (CD_3OD)



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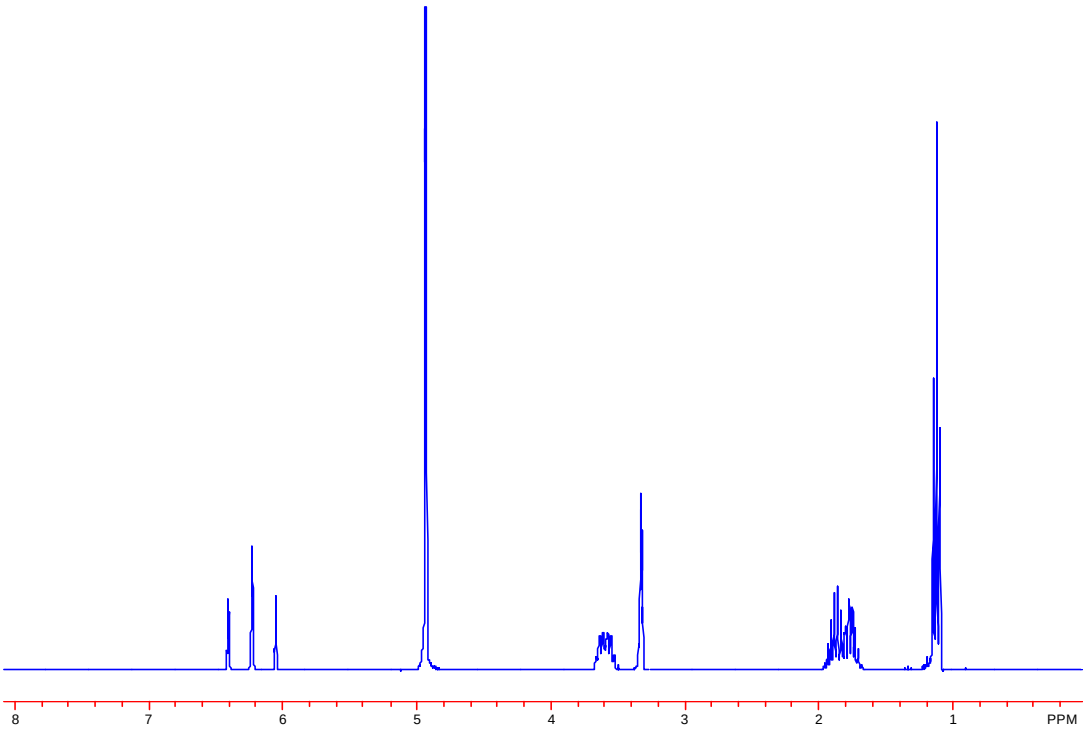
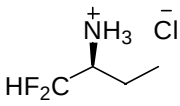


^{19}F NMR (CD_3OD)



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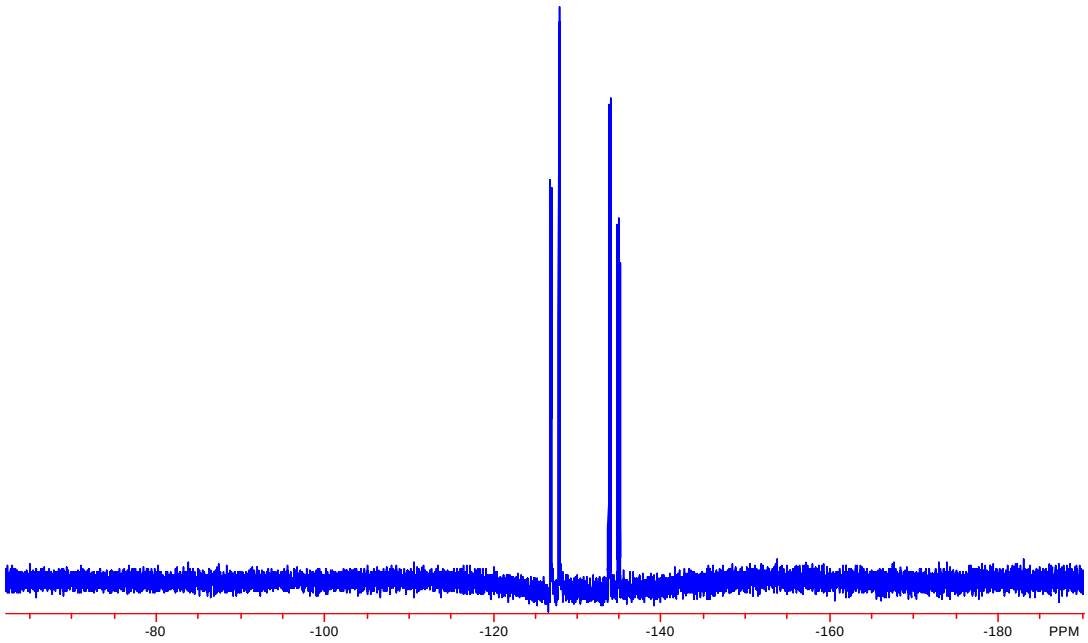
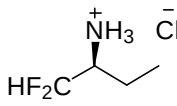


^{13}C NMR (CD_3OD)



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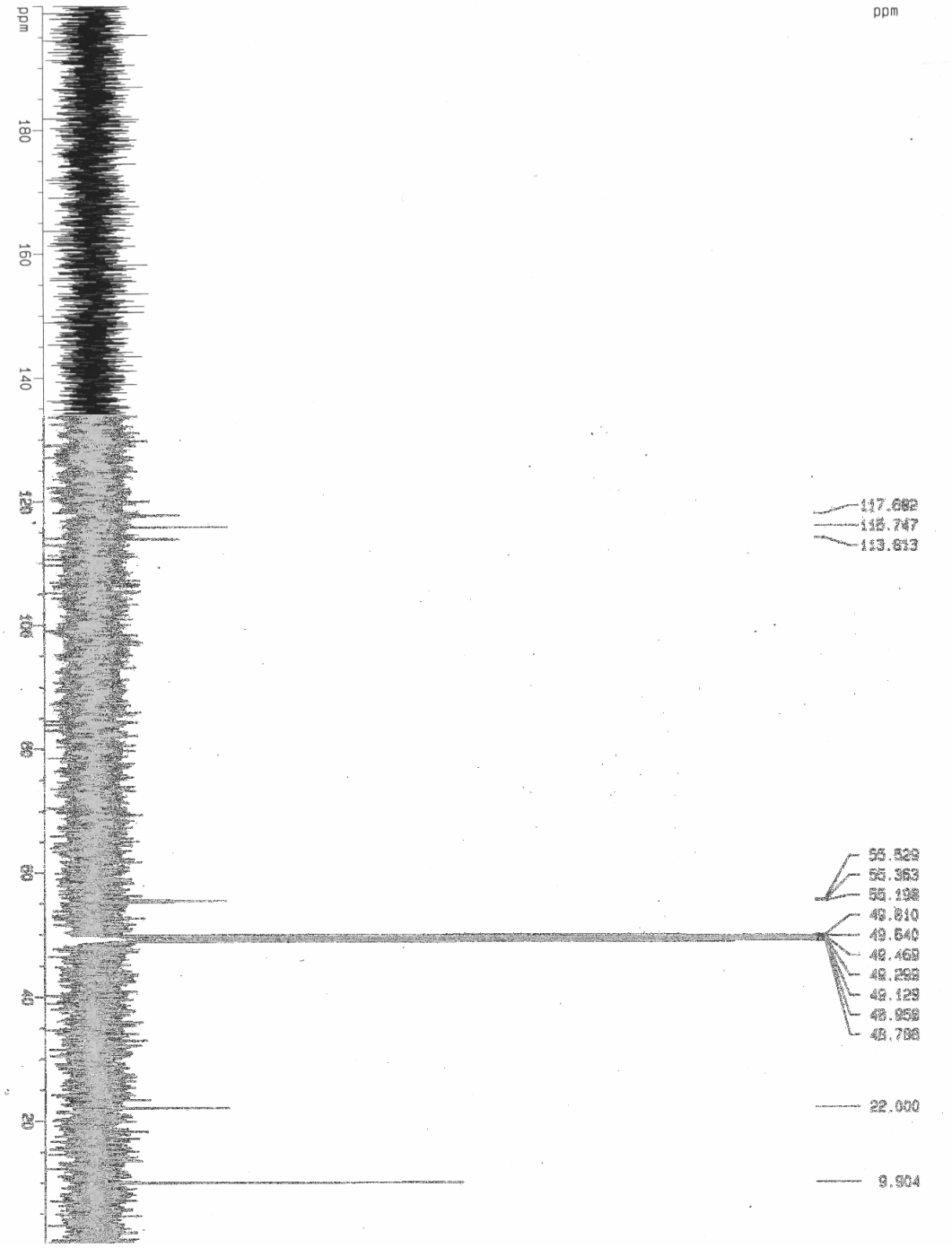
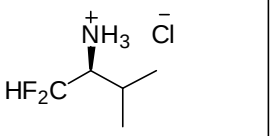


^{1}H NMR (CD_3OD)



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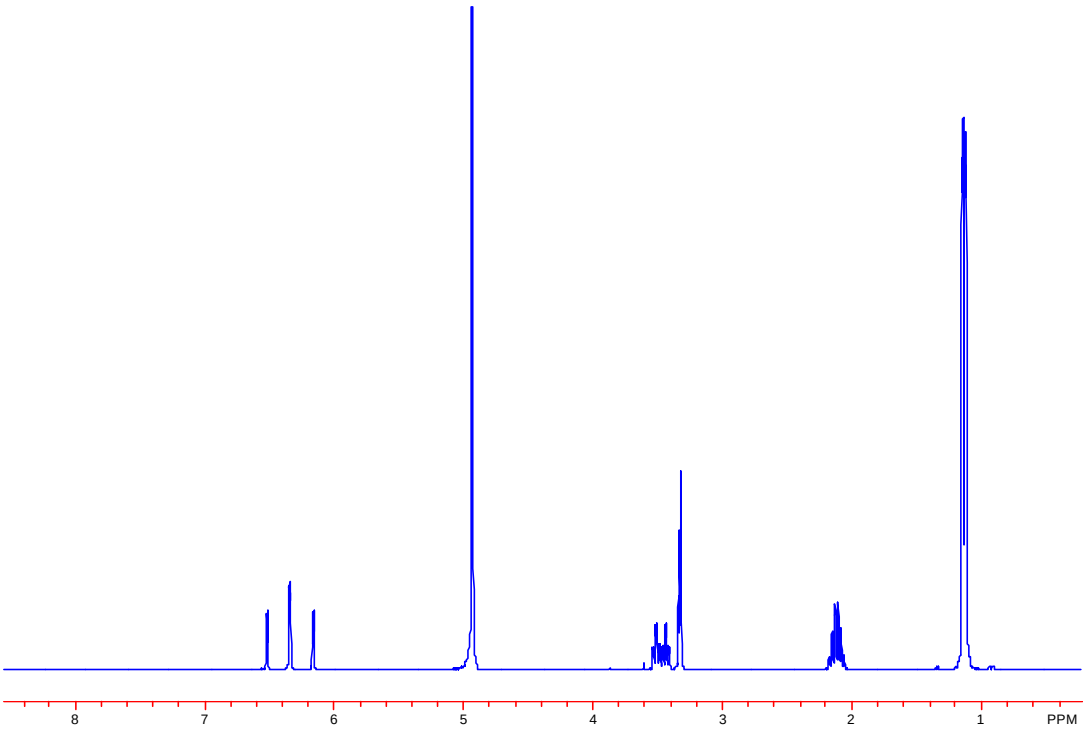
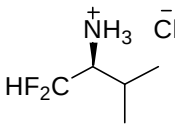


^{19}F NMR (CD_3OD)



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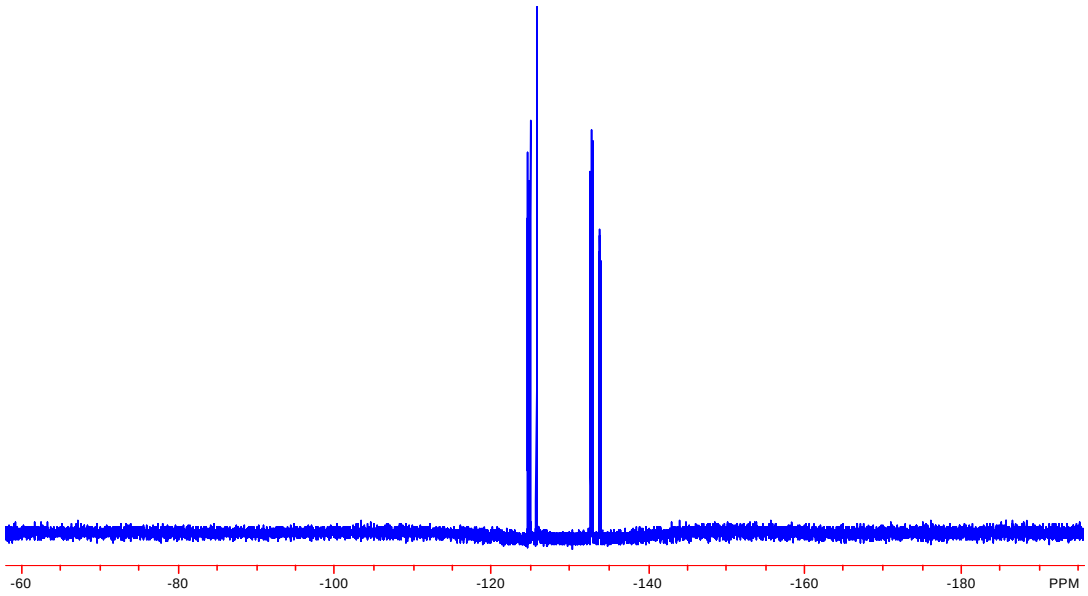
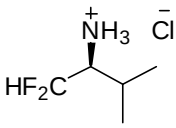


^{13}C NMR(CD_3OD)



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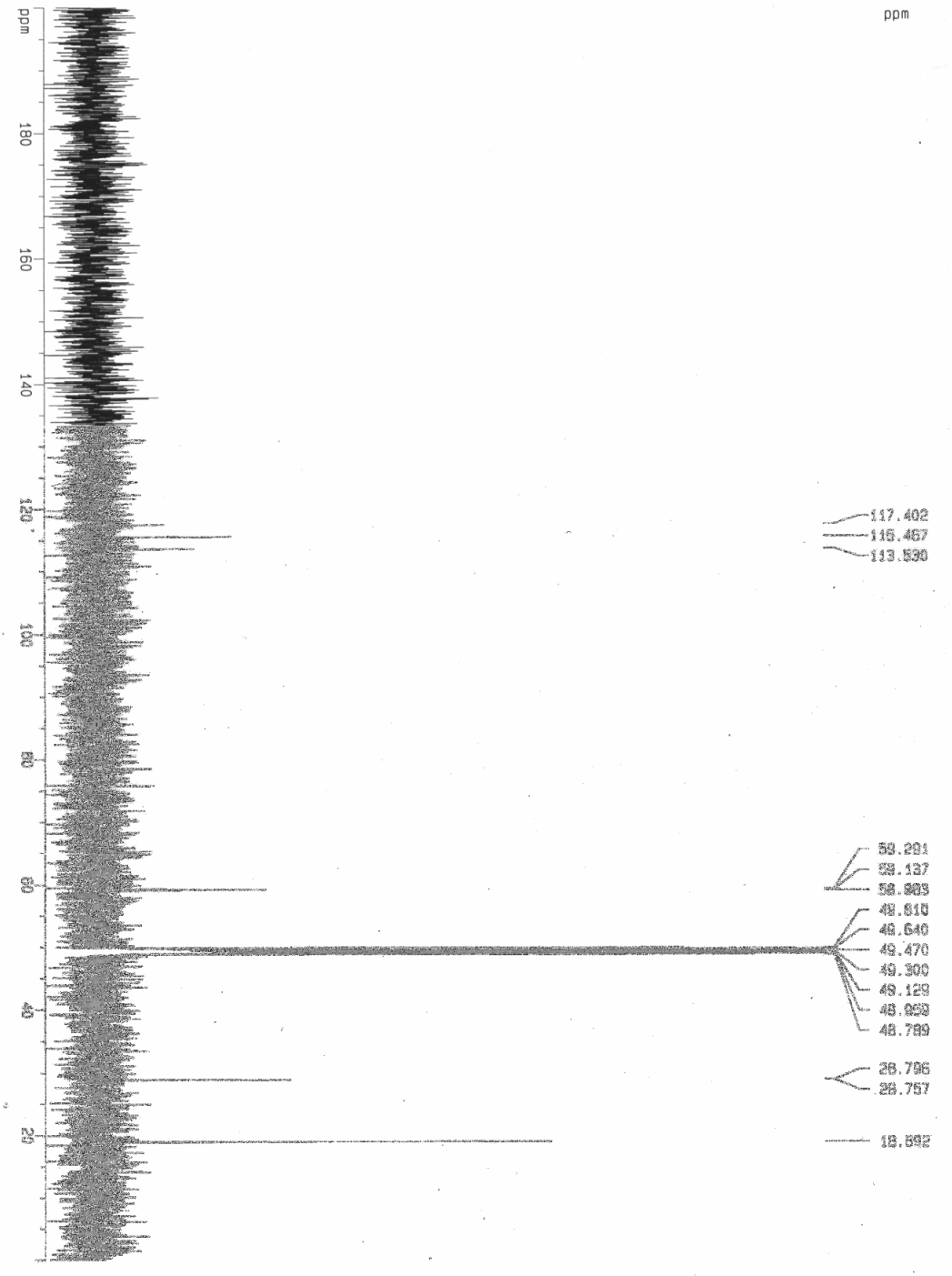
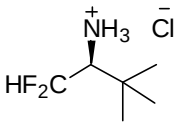


^{1}H NMR (CD_3OD)



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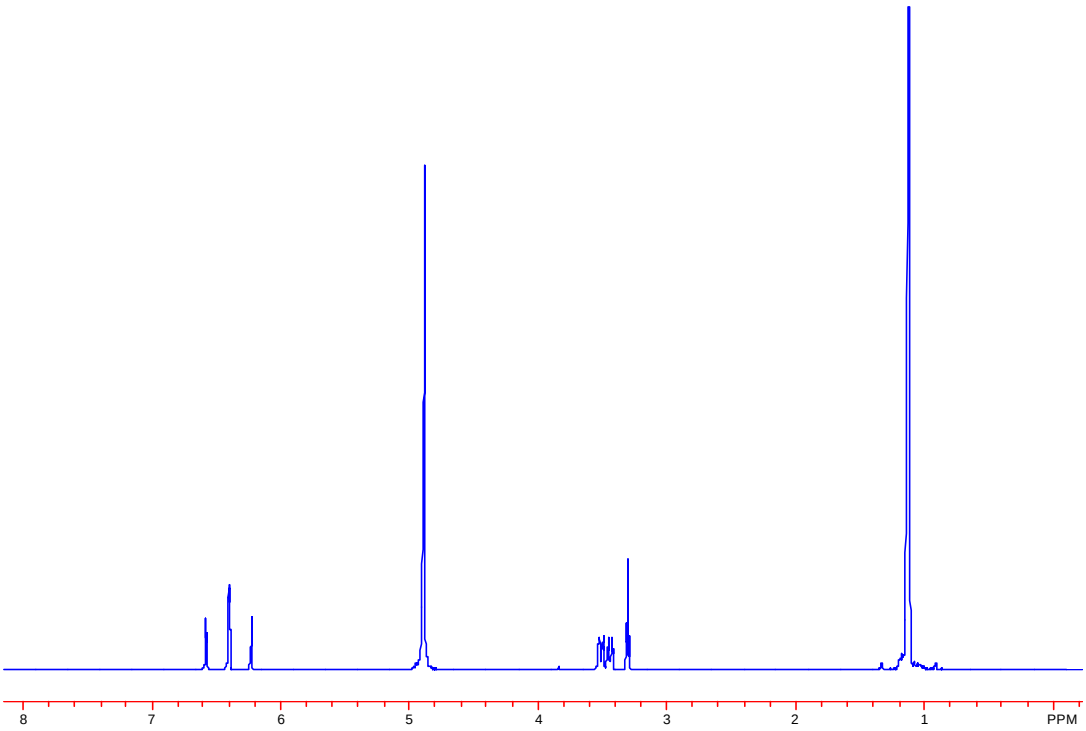
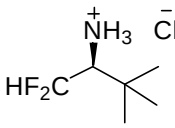


^{19}F NMR (CD_3OD)



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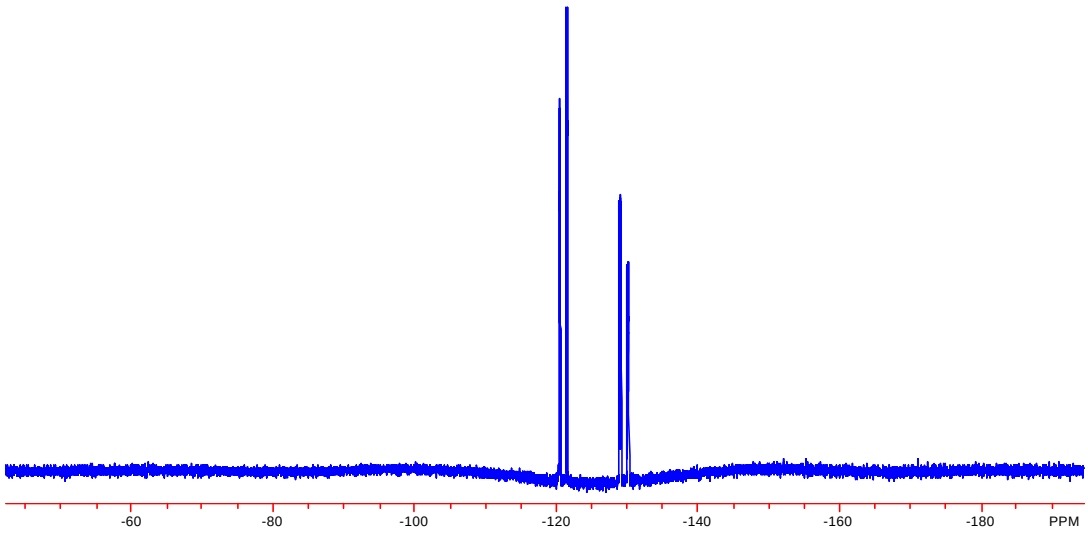

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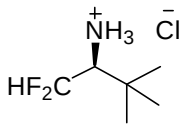

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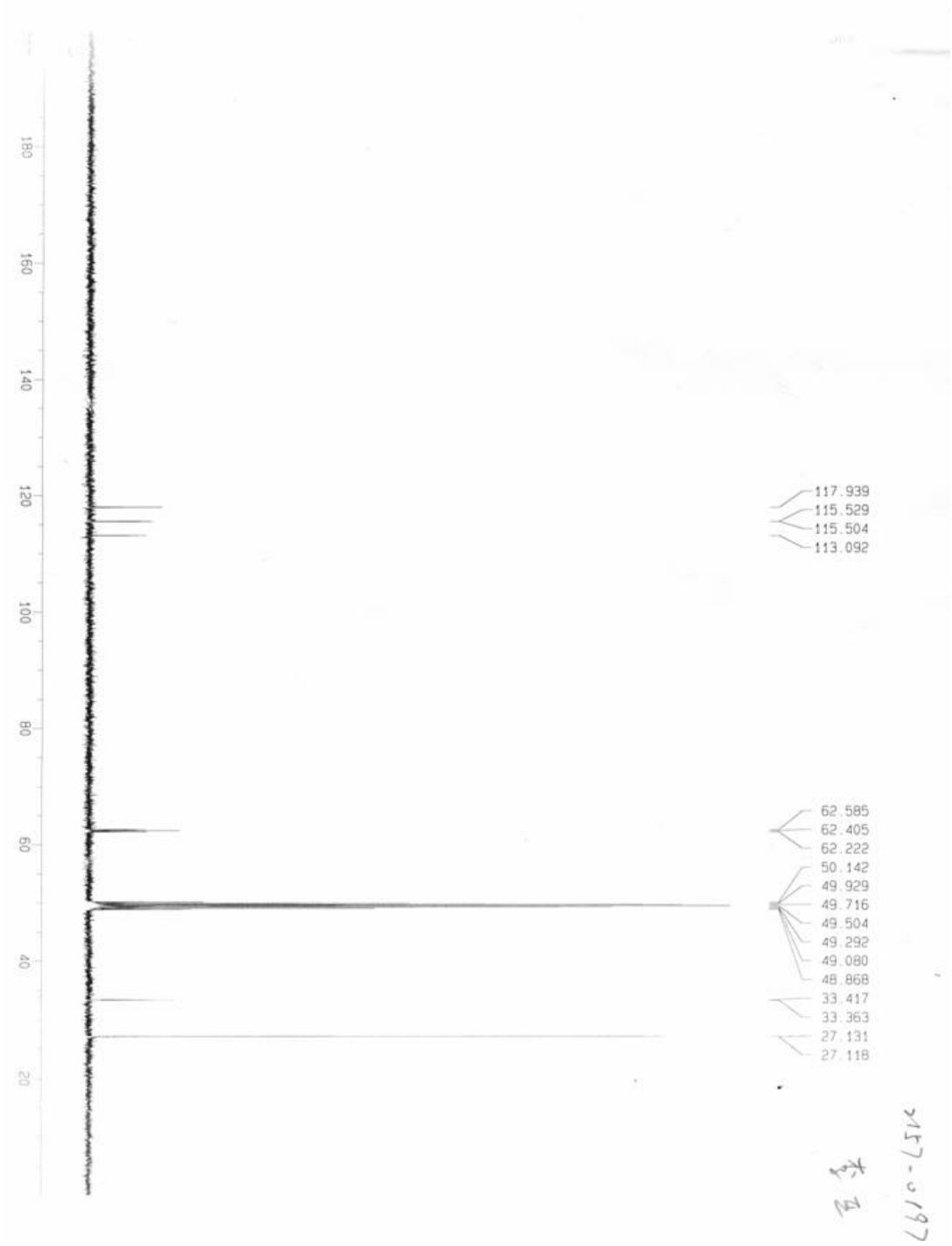
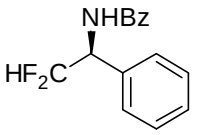
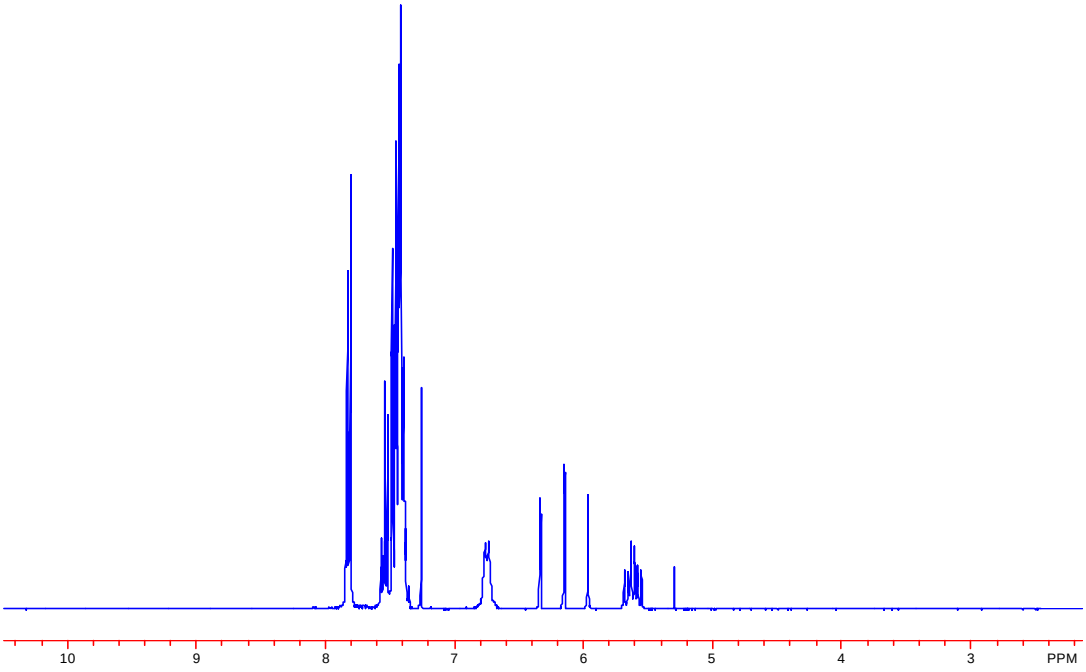


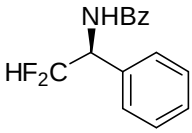
^{1}H NMR($CDCl_3$)



9



^{19}F NMR($CDCl_3$)



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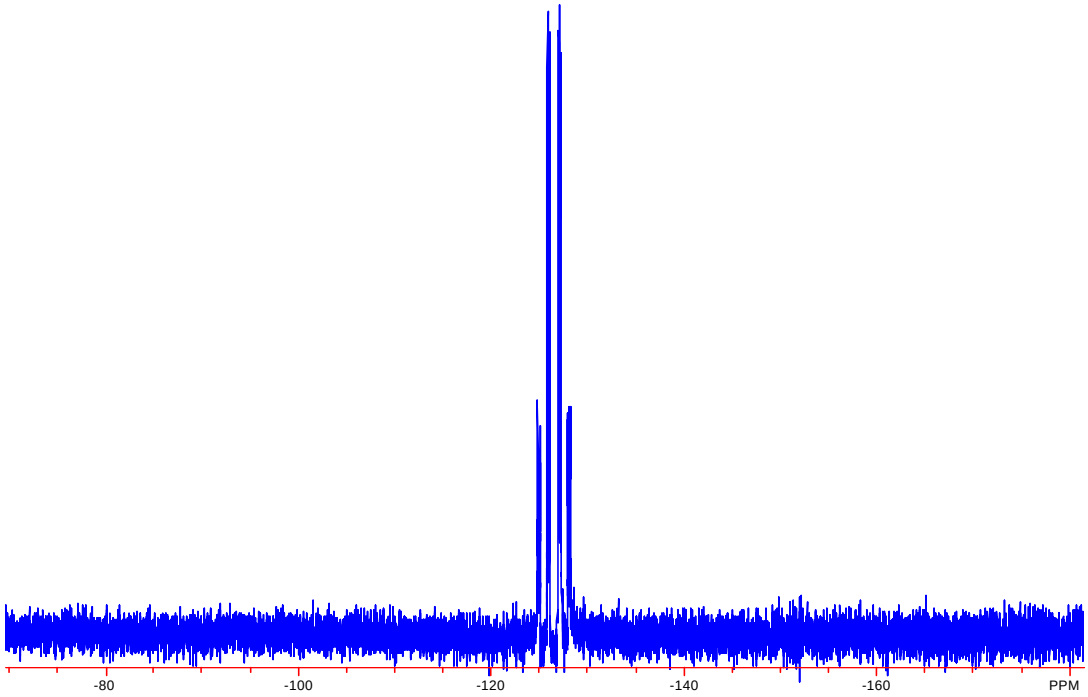
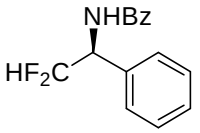


^{13}C NMR ($CDCl_3$)



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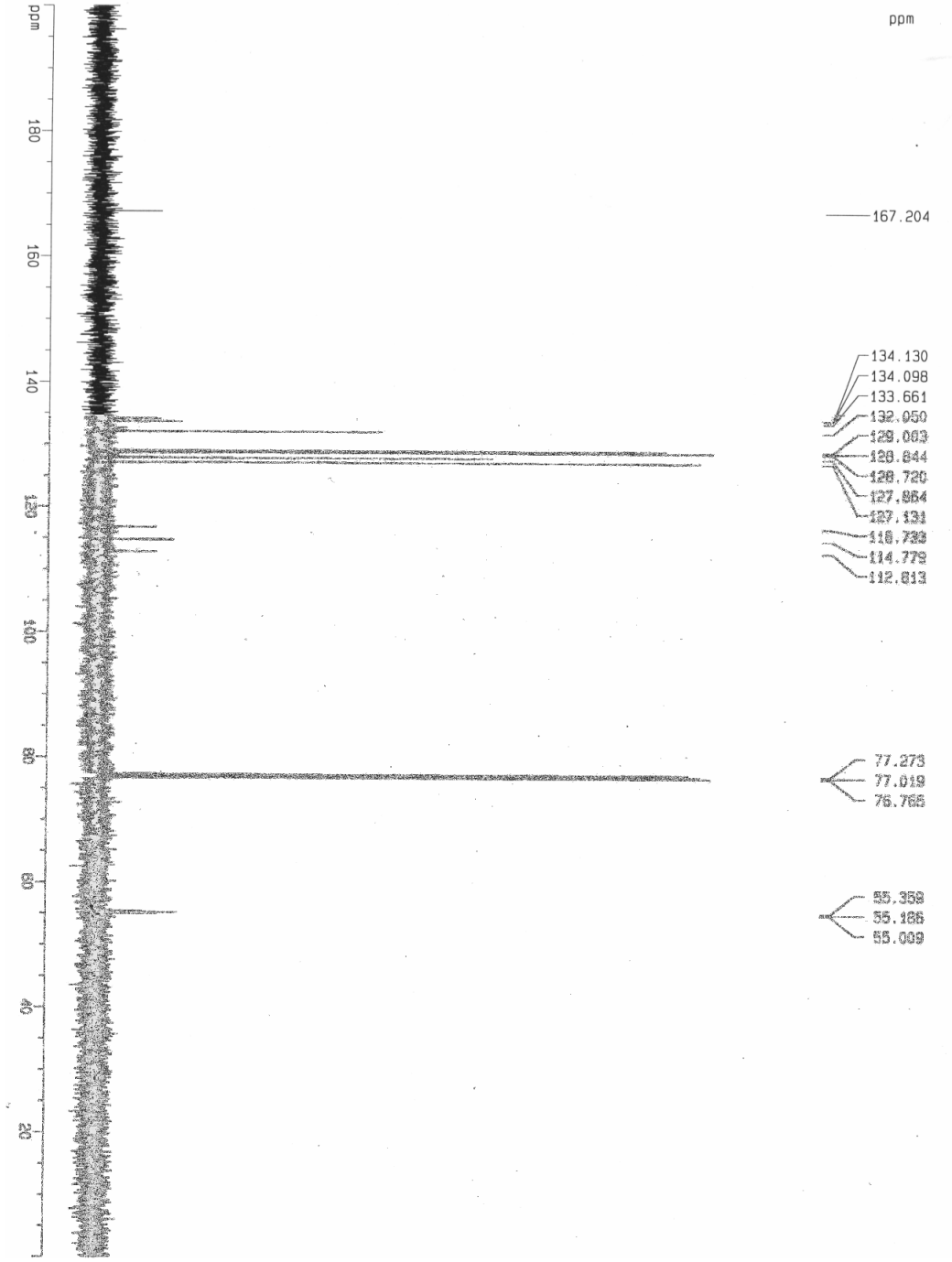
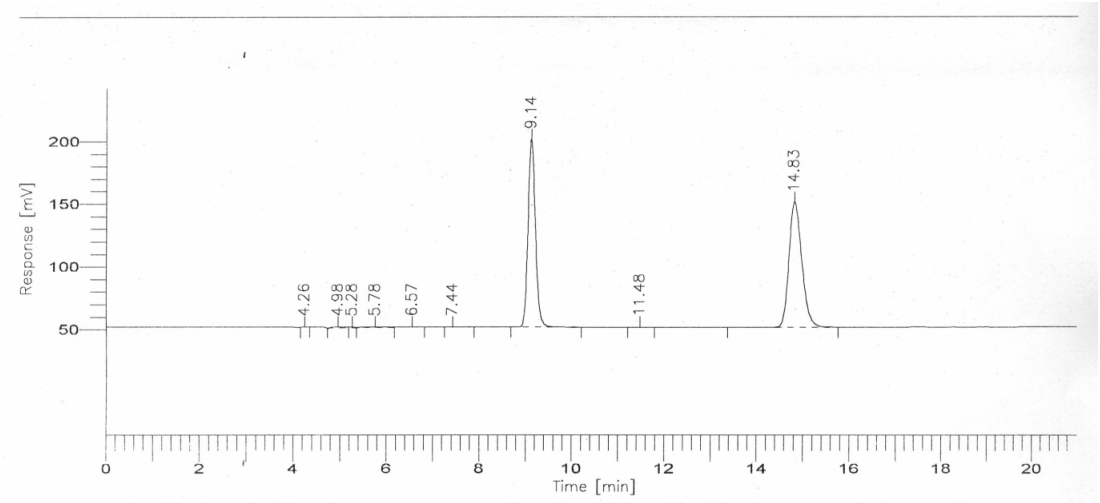


Determination of optical purity of **9** by chiral HPLC (Diacel Chiralpak AD-H column, 80:20 hexane/2-propanol; 0.7ml/min; 254nm; (S)-**9**, r_t=9.1min, (R)-**9**, r_t=14.8min):

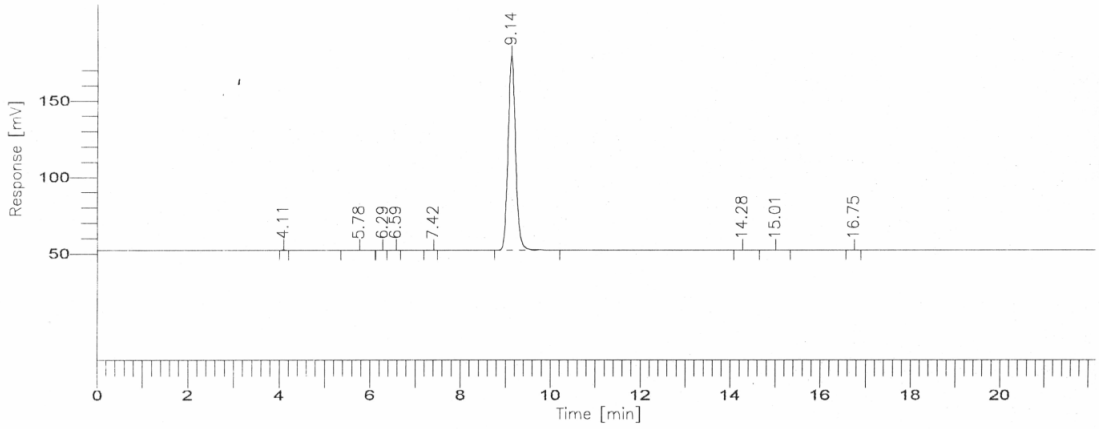
A: Racemic mixtures of (S)-9/(R)-9 as reference:



DEFAULT REPORT

Peak #	Time [min]	Area [uv*sec]]	Height [uv]	Area [%]	Norm Area [%]	BL	Area/Height [s]
1	4.257	1199.00	167.83	0.03	0.00	BB	7.14
2	4.981	23400.44	1063.98	0.64	0.00	BV	21.99
3	5.276	7748.76	869.30	0.21	0.00	VV	8.91
4	5.775	26450.87	632.11	0.73	0.00	VV	41.85
5	6.572	7413.44	214.30	0.20	0.00	VB	34.59
6	7.436	604.00	50.56	0.02	0.00	BB	11.95
7	9.138	1660332.00	149972.37	45.62	0.00	BB	11.07
8	11.483	777.50	48.71	0.02	0.00	BB	15.96
9	14.825	1911526.00	99773.65	52.52	0.00	BB	19.16
		3639452.00	252792.81	100.00	0.00		

B: Synthesized (S)-9:



DEFAULT REPORT

Peak #	Time [min]	Area [uv*sec]]	Height [uv]	Area [%]	Norm Area [%]	BL	Area/Height [s]
1	4.113	762.00	136.41	0.05	0.00	BB	5.59
2	5.775	612.00	24.24	0.04	0.00	BB	25.25
3	6.292	287.50	33.88	0.02	0.00	BV	8.49
4	6.586	306.00	27.87	0.02	0.00	VB	10.98
5	7.418	270.00	34.38	0.02	0.00	BB	7.85
6	9.140	1469366.00	127215.74	99.62	0.00	BB	11.55
7	14.281	650.00	30.43	0.04	0.00	BB	21.36
8	15.014	2511.50	146.68	0.17	0.00	BB	17.12
9	16.753	262.00	21.46	0.02	0.00	BB	12.21
		1475027.00	127671.09	100.00	0.00		

Complete references of citations [4], [5] and [10] in the article:

[4] M. Rowley, D. J. Hallett, S. Goodacre, C. Moyes, J. Crawforth, T. J. Sparey, S. Patel, R. Marwood, S. Patel, S. Thomas, L. Hitzel, D. O'Connor, N. Szeto, J. L. Castro, P. H. Hutson, A. M. MacLeod, *J. Med. Chem.* **2001**, *44*, 1603.

[5] M. B. van Niel, I. Collins, M. S. Beer, H. B. Broughton, S. K. F. Cheng, S. C. Goodacre, A. Heald, K. L. Locker, A. M. MacLeod, D. Morrison, C. R. Moyes, d. O'Connor, A. Pike, M. Rowley, M. G. N. Russell, B. Sohal, J. A. Stanton, S. Thomas, H. Verrier, A. P. Watt, J. L. Castro, *J. Med. Chem.* **1999**, *42*, 2087.

[10] S. Fustero, A. Navarro, B. Pina, J. G. Soler, A. Bartolome, A. Asensio, A. Simon, P. Bravo, G. Fronza, A. Volonterio, M. Zanda, *Org. Lett.* **2001**, *3*, 2621.